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The Patent Office
Concept House
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Newport
South Wales
NP10 8QQ

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Signed Andrew Gerry

Dated 26 November 2004

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Patents Form 1/77

Patents Act 1977
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07JAN04 E863486-1 D02934
P01/7700 0.00-0400196.2 NONE

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
South Wales
NP10 8QQ

1. Your reference 101294-1 GB

2. Patent application number *(The Patent Office will fill in this part)* 0400196.2

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

AstraZeneca AB
SE-151 85 Sodertalje
Sweden

Patents ADP number *(if you know it)* 78224420003

If the applicant is a corporate body, give the country/state of its incorporation Sweden

4. Title of the invention

THERAPEUTIC AGENTS

5. Name of your agent *(if you have one)* Thomas Kerr MILLER

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

AstraZeneca
Global Intellectual Property
P O Box 272
Mereside, Alderley Park
Macclesfield,
Cheshire SK10 4GR

Patents ADP number *(if you know it)* 21797301001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	53
Claim *(s)*	9
Abstract	1
Drawing *(s)*	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature S. A. Douglas Date 6/01/2004

12. Name and daytime telephone number of person to contact in the United Kingdom: Shirley Douglas - 01625 510057

Warning

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Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 08459 500505.

b) Write your answers in capital letters using black ink or you may type them.

c) If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.

d) If you have answered 'Yes' Patents Form 7/77 will need to be filed.

e) Once you have filled in the form you must remember to sign and date it.

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THERAPEUTIC AGENTS

Field of invention

The present invention relates to certain *N*-cycloalkyl, aryl or heteroaryl *N'*-quinolin-2-yl cycloalkyldiamines of formula I, to processes for preparing such compounds, to their use in the treatment of obesity, psychiatric and neurological disorders, and to pharmaceutical compositions containing them.

Background of the invention

Melanin concentrating hormone (MCH) is a cyclic peptide that was first isolated from fish over 15 years ago. In mammals, MCH gene expression is localised to the ventral aspect of the zona inserta and the lateral hypothalamic area (Breton et al., Molecular and Cellular Neurosciences, vol. 4, 271-284 (1993)). The latter region of the brain is associated with the control of behaviours such as eating and drinking, with arousal and with motor activity (Baker, B., Trends Endocrinol. Metab. 5: 120-126(1994), vol. 5, No. 3, 120-126 (1994)). Although the biological activity in mammals has not been fully defined, recent work has indicated that MCH promotes eating and weight gain (US 5,849,708). Thus, MCH and its agonists have been proposed as treatments for anorexia nervosa and weight loss due to AIDS, renal disease, or chemotherapy. Similarly, antagonists of MCH can be used as a treatment for obesity and other disorders characterised by compulsive eating and excessive body weight. MCH projections are found throughout the brain, including the spinal cord, an area important in processing nociception, indicates that agents acting through MCH1r, such as compounds of formula I, will be useful in treating pain.

Two receptors for MCH (MCH1r (Shimomura et al. Biochem Biophys Res Commun 1999 Aug 11;261(3):622-6) & MCH2r (Hilol et al. J Biol Chem. 2001 Jun 8;276(23):20125-9)) have been identified in humans, while only one (MCH1r) is present in rodent species (Tan et al. Genomics. 2002 Jun;79(6):785-92). In mice lacking MCH1r, there is no increased feeding response to MCH, and a lean phenotype is seen, suggesting that this receptor is

responsible for mediating the feeding effect of MCH (Marsh et al. Proc Natl Acad Sci U S A. 2002 Mar 5;99(5):3240-5). In addition, MCH receptor antagonists have been demonstrated to block the feeding effects of MCH (Takekawa et al. Eur J Pharmacol. 2002 Mar 8;438(3):129-35), and to reduce body weight & adiposity in diet-induced obese rats (Borowsky et al. Nat Med. 2002 Aug;8(8):825-30). The conservation of distribution and sequence of MCH1r suggest a similar role for this receptor in man and rodent species. Hence, MCH receptor antagonists have been proposed as a treatment for obesity and other disorders characterised by excessive eating and body weight.

US 3,020,283 discloses that certain *N,N'*- bis lepid-2-yl 1,x-diamino C_{1-x} alkanes where x is an integer from 2 to 12 and *N,N'*- bis lepid-2-yldiaminocycloalkanes are useful as anthelmintics.

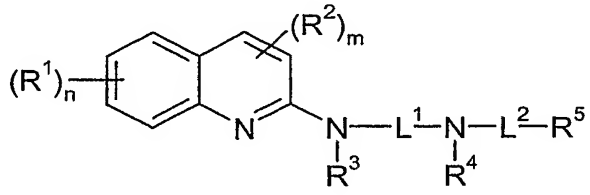
US 5,093,333 discloses certain *N*- substituted (cyclicaminoalkyl) 2-aminoquinolines which are useful for treating hypofunction of the cholinergic system and therefore useful in treating dementias involving the cholinergic system.

US 4,203,988 discloses certain pyridinyl and quinolinyl ureas which are useful in treating gastric secretion.

WO99/55677 discloses 2-(aminoalkylamino)quinolin-4-ones which are useful as anti-bacterial agents.

WO02/58702 discloses substituted 2-(aminoalkyl amino) quinolines which are antagonists of urotensin II which are alleged to be useful in treating cardiovascular diseases characterised by excessive or abnormal vasoconstriction and myocardial dysfunction and also in diseases of the CNS for example addiction, schizophrenia, anxiety and depression and metabolic diseases such as diabetes.

Co-pending application PCT/GB03/02884 discloses compounds of the general formula (I)



I

wherein

R^1 represents a C_{1-4}alkoxy group optionally substituted by one or more fluoro or a C_{1-4}alkyl group optionally substituted by one or more fluoro;

n represents 0 or 1;

R^2 represents a C_{1-4}alkyl group optionally substituted by one or more fluoro or a C_{1-4}alkoxy group optionally substituted by one or more fluoro ;

m represents 0 or 1;

R^3 represents H or a C_{1-4}alkyl group;

L^1 represents an alkylene chain $(CH_2)_r$ in which r represents 2 or 3 or L^1 represents a cyclohexyl group wherein the two nitrogens bearing R^3 and R^4, respectively, are linked to the cyclohexyl group either via the 1,3 or the 1,4 positions of the cyclohexyl group or L^1 represents a cyclopentyl group wherein the two nitrogens bearing R^3 and R^4, respectively, are linked to the cyclopentyl group via the 1,3 position of the cyclopentyl group and additionally when R^5 represents 9, 10-methanoanthracen-9(10*H*)-yl the group $-L^1-N(R^4)-$ together represents a piperidyl ring which is linked to L^2 through the piperidinyl nitrogen and to N-R^3 via the 4 position of the piperidyl ring with the proviso that when R^5 represents 9, 10-methanoanthracen-9(10*H*)-yl then r is only 2;

R^4 represents H or a C_{1-4}alkyl group optionally substituted by one or more of the following: an aryl group or a heteroaryl group;

L^2 represents a bond or an alkylene chain $(CH_2)_s$ in which s represents 1, 2 or 3 wherein the alkylene chain is optionally substituted by one or more of the following: a C_{1-4}alkyl group, phenyl or heteroaryl;

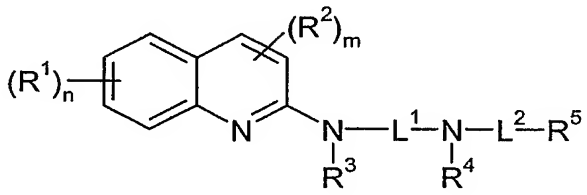
R^5 represents aryl (wherein aryl means phenyl, naphthyl, or 9, 10-methanoanthracen-9(10*H*)-yl, each of which is optionally substituted by one or more of the following: halo, a C_{1-4}alkyl group, phenyl, or a group of formula NR^6R^7 wherein R^6 and R^7 are independently selected from H or a C_{1-4}alkyl group), a heterocyclic group (wherein the term "heterocyclic group" as used herein means thienyl, furyl, pyridyl, pyrrolyl, quinolinyl, indolyl, benzofuranyl or benzo[*b*]thienyl each of which is optionally substituted by one or more of the following: halo, a C_{1-4}alkyl group, a C_{1-4}acyl group or nitro) or a C_{3-8}cycloalkyl group which is optionally fused to a phenyl or to a heteroaryl group (wherein the term "heteroaryl" means thienyl, furyl or pyrrolyl);
as well as optical isomers and racemates thereof as well as pharmaceutically acceptable salts, thereof;
with a first proviso that when n is 0, and m is 1 and R^2 is methyl located at the 4-position of the quinoline ring, and R^3 is H and R^4 is H and L^1 is $(CH_2)_2$ or $(CH_2)_3$ or 1,4-cyclohexyl, and L^2 is a bond then R^5 is not 4-methylquinolin-2-yl;
and with a second proviso that when n is 0, and m is 0 or 1 and R^2 is a C_{1-3}alkoxy group located at the 4-position of the quinoline ring, and R^3 is H or a C_{1-3}alkyl group and R^4 is H or a C_{1-3}alkyl group and L^1 is $(CH_2)_3$ and L^2 is methylene optionally substituted by one or more C_{1-3}alkyl groups or phenyl then R^5 is not phenyl, thienyl or indolyl optionally substituted by one, two or three C_{1-4}alkyl groups or halo which are MCH1r antagonists which are useful in treating obesity and related disorders, psychiatric disorders, neurological disorders and pain. The compounds claimed and disclosed in this application are disclaimed from the present invention.

There is an unmet need for MCH receptor antagonists that are more potent, more selective, more bioavailable and less toxic than known compounds in this field.

The present invention provides additional compounds that are MCH1r antagonists which are useful in treating obesity and related disorders, psychiatric disorders, neurological disorders and pain.

Description of the invention

The invention relates to compounds of the general formula (I)



I

wherein

R^1 represents a C_{1-4} alkoxy group optionally substituted by one or more fluoro, a C_{1-4} alkyl group optionally substituted by one or more fluoro, halo, cyano, a group NR^aR^b in which R^a and R^b independently represent H or a C_{1-4}alkyl group or R^a and R^b together with the nitrogen atom to which they are attached represent a saturated 3 to 7 membered heterocyclic ring optionally including an O atom (forming e.g. a morpholine ring), a group $CONR^cR^d$ in which R^c and R^d independently represent H or a C_{1-4}alkyl group or R^c and R^d together with the nitrogen atom to which they are attached represent a saturated 3 to 7 membered heterocyclic ring,

n represents 0, 1, 2 or 3 ;

R^2 represents a C_{1-4}alkyl group optionally substituted by one or more fluoro or a C_{1-4}alkoxy group optionally substituted by one or more fluoro, a group NR^aR^b in which R^a and R^b independently represent H or a C_{1-4} alkyl group or R^a and R^b together with the nitrogen atom to which they are attached represent a saturated 3 to 7 membered heterocyclic ring optionally including an O (forming e.g. a morpholine ring), a group

$CONR^cR^d$ in which R^c and R^d independently represent H or a C_{1-4}alkyl group or R^c and R^d together with the nitrogen atom to which they are attached represent a saturated 3 to 7 membered heterocyclic ring;

m represents 0 or 1;

R^3 represents H or a C_{1-4} alkyl group;

L^1 represents a $(CH_2)_pC_{3-10}$ cycloalkyl group in which p is 0 or 1 and in which the cycloalkyl group may be monocyclic or bicyclic and optionally may be bridged provided that the two nitrogens bearing R^3 and R^4, respectively, are not linked to the same carbon atom, and wherein one of the carbons may be replaced by O or, alternatively, the group -$N(R^3)$ -L^1- or the group L^1-$N(R^4)$ together represent a saturated bicyclic heterocyclic ring containing from 2 to 9 carbon atoms and the nitrogen bearing R^3 or R^4 respectively or alternatively the group -$N(R^3)$ -L^1- $N(R^4)$ together represents a saturated heterocyclic ring containing from 6 to 9 carbon atoms and the nitrogens bearing R^3 and R^4 which is bicyclic;

R^4 represents H or a C_{1-4} alkyl group optionally substituted by one or more of the following: fluoro or C_{1-4} alkoxy optionally substituted by one or more fluoro;

L^2 represents an alkylene chain $(CH_2)_s$ in which s represents 1, 2 or 3 wherein the alkylene chain is optionally substituted by one or more of the following: fluoro or C_{1-4} alkyl;
or L^2 may also represent a 5-6 membered carbocyclic ring fused to R^5,

R^5 represents phenyl or naphthyl or a heterocyclic group selected from thienyl, furyl, pyridyl, pyrrolyl, quinolinyl, indolyl, benzofuranyl, benzo[*b*]thienyl, imidazolyl, benzimidazolyl, thiazolyl, thiadiazolyl, pyrimidinyl, pyrazolyl, oxazolyl, imidazo[1,2-*a*]pyridine, 5*H*-pyrrolo[2,3-*b*]pyrazine, 1*H*-pyrrolo[3,2-*c*]pyridine, 1*H*-pyrrolo[2,3-*c*]pyridine, 1*H*-pyrrolo[2,3-*b*]pyridine, *1H*-indazole wherein each R^5 is optionally substituted by one or more of the following: cyano, halo, a C_{1-4} alkyl group optionally

substituted by one or more fluoro, a C_{1-4} alkoxy group optionally substituted by one or more fluoro, or by a group $S(O)_aR^y$ in which a is 0, 1 or 2 and R^y is phenyl optionally substituted by cyano, halo, a C_{1-4}alkyl group optionally substituted by one or more fluoro or a C_{1-4}alkoxy group optionally substituted by one or more fluoro, or by a group $(CH_2)_zR^z$ in which z is 0 or 1 and R^z represents phenyl or a heterocyclic group selected from thienyl, pyridyl, thiazolyl, pyrazolyl, wherein each R^z is optionally substituted by one or more of the following:cyano, halo, a C_{1-4} alkyl group optionally substituted by one or more fluoro, or a C_{1-4}alkoxy group optionally substituted by one or more fluoro;
as well as optical isomers and racemates thereof as well as pharmaceutically acceptable salts, thereof;

with the proviso that when
R^1 represents a C_{1-4}alkoxy group optionally substituted by one or more fluoro or a C_{1-4}alkyl group optionally substituted by one or more fluoro; and
n represents 0 or 1; and
R^2 represents a C_{1-4}alkyl group optionally substituted by one or more fluoro or a C_{1-4}alkoxy group optionally substituted by one or more fluoro ; and
m represents 0 or 1; and
R^3 represents H or a C_{1-4}alkyl group; and
L^1 represents a cyclohexyl group wherein the two nitrogens bearing R^3 and R^4, respectively, are linked to the cyclohexyl group either via the 1,3 or the 1,4 positions of the cyclohexyl group or L^1 represents a cyclopentyl group wherein the two nitrogens bearing R^3 and R^4, respectively, are linked to the cyclopentyl group via the 1,3 position of the cyclopentyl group; and
L^2 represents an alkylene chain $(CH_2)_s$ in which s represents 1, 2 or 3 wherein the alkylene chain is optionally substituted by one or more of the following: a C_{1-4}alkyl group; and
R^5 represents aryl wherein aryl means phenyl or naphthyl each of which is optionally substituted by one or more of the following: halo, a C_{1-4}alkyl group or phenyl, or
R^5 represents a heterocyclic group wherein the term heterocyclic group means thienyl, furyl, pyridyl, pyrrolyl, quinolinyl, indolyl, benzofuranyl or benzo[*b*]thienyl each of which is optionally substituted by one or more of the following: halo or a C_{1-4}alkyl group ;

or L^2 represents a C_{5-6}cycloalkyl group which is fused to an R^5 which is phenyl or a heteroaryl group selected from thienyl, furyl or pyrrolyl;
then R^4 does not represent H or a C_{1-4}alkyl group.

Particular groups now follow in which some of R^1, R^2, R^3, R^4, R^5, L^1, L^2, n and m in compounds of formula I are further defined. It will be understood that such group definitions may be used where appropriate with any of the other group definitions, claims or embodiments defined hereinbefore or hereinafter.

In a particular group of compounds of formula I, n is 1 and R^1 represents methoxy, fluoro, chloro or dimethylamino. In particular R^1 is attached at either the 6 or 7 position of the quinoline ring. In particular when n is 2, R^1 is independently selected from methoxy, fluoro, chloro or dimethylamino and and is attached at the 6 and 7 position.

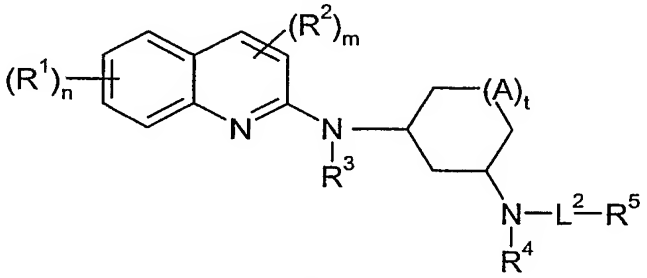
In a particular group of compounds of formula I, L^1 represents a monocyclic $(CH_2)_pC_{5-6}$ cycloalkyl group in which p is 0 or 1 wherein there are 3 carbon atoms between the two nitrogens bearing R^3 and R^4, respectively, wherein one of the carbons of the cycloalkyl group may be replaced by O or the group $-N(R^3)-L^1-$, or the group L^1-$N(R^4)$, together represent a saturated heterocyclic ring containing from 4 to 6 carbon atoms and the nitrogen bearing R^3 or R^4 respectively.

Particularly in compounds of formula I, p is 0 and L^1 is 1,3-cyclopentyl.
Particularly in compounds of formula I, p is 0 L^1 is 1,3-cyclohexyl.

In a particular group of compounds of formula I, R^5 represents a heterocyclic group selected from imidazolyl, benzimidazolyl, thiazolyl, thiadiazolyl, pyrimidinyl, pyrazolyl, oxazolyl, imidazo[1,2-*a*]pyridine, 5*H*-pyrrolo[2,3-*b*]pyrazine, 1*H*-pyrrolo[3,2-*c*]pyridine, 1*H*-pyrrolo[2,3-*c*]pyridine, 1*H*-pyrrolo[2,3-*b*]pyridine, *1H*-indazole wherein each R^5 is optionally substituted by one or more of the following: cyano, halo, a C_{1-4} alkyl group optionally substituted by one or more fluoro, a C_{1-4} alkoxy group optionally substituted by one or more fluoro, or by a group $S(O)_aR^y$ in which a is 0, 1 or 2 and R^y is phenyl optionally substituted by cyano, halo, a C_{1-4}alkyl group optionally substituted by one or

more fluoro or a C_{1-4}alkoxy group optionally substituted by one or more fluoro, or by a group $(CH_2)_zR^z$ in which z is 0 or 1 and R^z represents phenyl or a heterocyclic group selected from thienyl, pyridyl, thiazolyl, pyrazolyl, wherein each R^z is optionally substituted by one or more of the following:cyano, halo, a C_{1-4} alkyl group optionally substituted by one or more fluoro, or a C_{1-4}alkoxy group optionally substituted by one or more fluoro.

A further particular group of compounds of formula I, is represented by formula IA



IA

in which

R^1 represents chloro, fluoro, methoxy or a group NR^aR^b in which R^a and R^b independently represent H or a C_{1-4}alkyl group.

n represents 0 or 1, 2 and when n=1 the substituent is attached to either position 6 or 7;

R^2 represents a C_{1-4}alkyl group or a C_{1-4}alkoxy group optionally substituted by one or more fluoro, a group NR^aR^b in which R^a and R^b independently represent H or a C_{1-4}alkyl group or R^a and R^b together with the nitrogen atom to which they are attached represent a saturated 3 to 7 membered heterocyclic ring optionally including an O (forming e.g. a morpholine ring), a group $CONR^cR^d$ in which R^c and R^d independently represent H or a C_{1-4}alkyl group or R^c and R^d together with the nitrogen atom to which they are attached represent a saturated 3 to 7 membered heterocyclic ring;

m represents 0 or 1;

R^3 represents H;

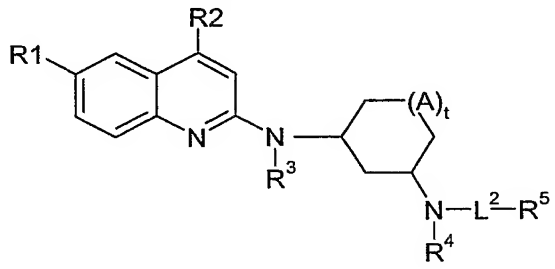
A represents CH_2 and t is 0 or 1;

R^4 represents H;

L^2 represents CH_2, $C(CH_3)_2$ or CF_2; and

R^5 represents aryl or a heterocyclic group selected from thienyl, furyl, pyridyl, pyrrolyl, quinolinyl, indolyl, benzofuranyl, benzo[*b*]thienyl, imidazolyl, benzimidazolyl, thiazolyl, thiadiazolyl, pyrimidinyl, pyrazolyl, oxazolyl, imidazo[1,2-*a*]pyridine, 5*H*-pyrrolo[2,3-*b*]pyrazine, 1*H*-pyrrolo[3,2-*c*]pyridine, 1*H*-pyrrolo[2,3-*c*]pyridine, 1*H*-pyrrolo[2,3-*b*]pyridine, *1H*-indazole each of which is optionally substituted by one or more of the following: cyano, halo, a C_{1-4} alkyl group optionally substituted by one or more fluoro, a C_{1-4} alkoxy group optionally substituted by one or more fluoro, or by a group $S(O)_aR^y$ in which a is 0, 1 or 2 and R^y is phenyl optionally substituted by cyano, halo, a C_{1-4}alkyl group optionally substituted by one or more fluoro or a C_{1-4}alkoxy group optionally substituted by one or more fluoro, or by a group $(CH_2)_zR^z$ in which z is 0 or 1 and R^z represents phenyl or a heterocyclic group selected from thienyl, pyridyl, thiazolyl, pyrazolyl, wherein each R^z is optionally substituted by one or more cyano, halo, a C_{1-4} alkyl group optionally substituted by one or more fluoro, a C_{1-4}alkoxy group optionally substituted by one or more fluoro as well as optical isomers and racemates thereof as well as pharmaceutically acceptable salts thereof.

Another particular group of compounds of formula I is represented by formula IB



IB

in which

R^1 represents H, methoxy, dimethylamino, chloro or fluoro;

R^2 represents H, a C_{1-4}alkyl group or a C_{1-4} alkoxy group optionally substituted by one or more fluoro, a group NR^aR^b in which R^a and R^b independently represent H or a C_{1-4}alkyl group or R^a and R^b together with the nitrogen atom to which they are attached represent a saturated 3 to 7 membered heterocyclic ring optionally including an O (forming e.g. a morpholine ring), a group $CONR^cR^d$ in which R^c and R^d independently represent H or a C_{1-4}alkyl group or R^c and R^d together with the nitrogen atom to which they are attached represent a saturated 3 to 7 membered heterocyclic ring;

R^3 represents H;

A represents CH_2 and t is 0 or 1;

R^4 represents H;

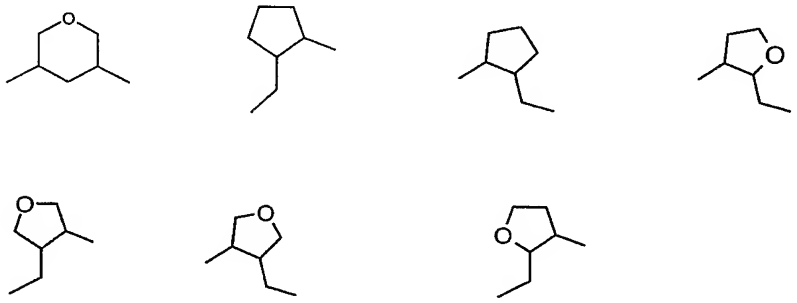
L^2 represents CH_2, $C(CH_3)_2$ or CF_2; and

R^5 represents 2-thienyl, 3-thienyl, indol-3-yl, 2-pyrrolyl, 5-pyrimidinyl, 4-thiadiazolyl, pyrazolyl, or quinolin-2-yl each of which is optionally substituted by one or more of the following: cyano, halo, a C_{1-4} alkyl group optionally substituted by one or more fluoro, a C_{1-4} alkoxy group optionally substituted by one or more fluoro and in addition when R^5 is 2-thienyl it is optionally additionally substituted by pyridyl, 2-thienyl or 3-pyrazolyl each of which is optionally substituted by halo or a C_{1-4} alkyl group optionally substituted by one or more fluoro and when R^5 is indol-3-yl it is optionally additionally substituted by 1-(thiazol-5-yl) methyl which is optionally substituted by halo.

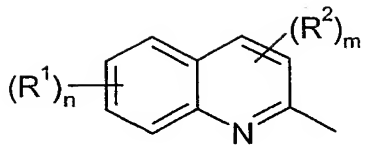
Particularly in compounds of formula IA and IB the two nitrogen atoms are in a trans orientation on the cycloalkyl ring.

More particularly in compounds of formula IA and IB the stereochemistry of the cycloalkyl carbon atoms to which the nitrogen atoms are attached is S, S.

Particularly in compounds of formula I, L^1 is selected from:

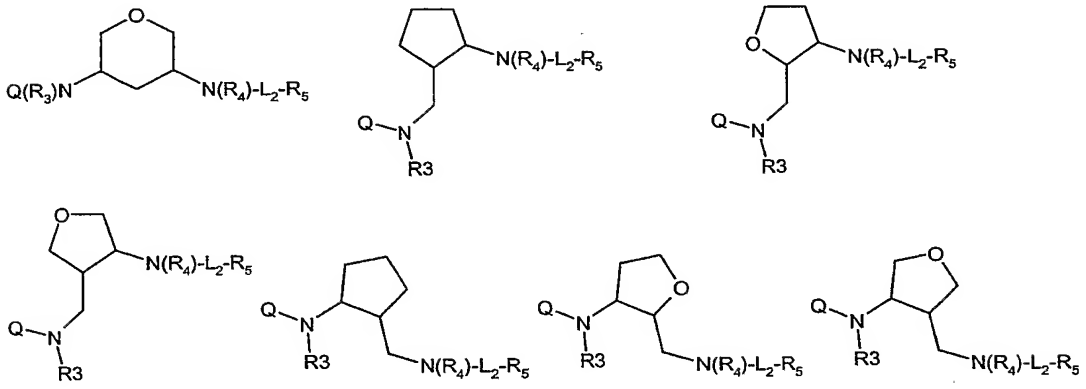


It will be understood that in the above the free bond to the left of the page is attached to the nitrogen bearing R^3 and the free bond to the right of the page is attached to the nitrogen bearing R^4. For the avoidance of doubt when Q represents



Q

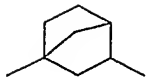
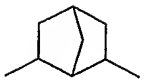
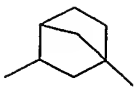
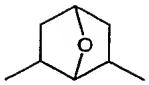
particular compounds of the invention are

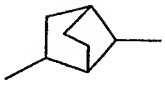
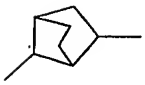


in which Q, R^3, L^2 and R^5 are as previously defined.

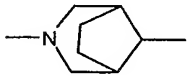
In a particular group of compounds of formula I, L^1 represents a $(CH_2)_pC_{7-10}$ cycloalkyl group in which p is 0 or 1 and in which the cycloalkyl group is fused or bridged bicyclic provided that the two nitrogens bearing R^3 and R^4, respectively, are not linked to the same carbon atom, and wherein one of the carbons may be replaced by O or, alternatively, the group $-N(R^3)-L^1-$ or the group $L^1-N(R^4)$ together represent a saturated bicyclic heterocyclic ring containing from 2 to 9 carbon atoms and the nitrogen bearing R^3 or R^4 respectively or alternatively the group $-N(R^3)-L^1-N(R^4)$ together represents a saturated heterocyclic ring containing from 6 to 9 carbon atoms and the nitrogens bearing R^3 and R^4 which is bicyclic and R^1, R^2, R^3, R^4, R^5, L^2, m and n are as defined above.

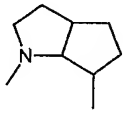
Examples where L^1 is bicyclic include particularly

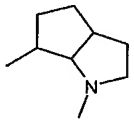



Examples where -N(R^3) -L^1- together represents a saturated heterocyclic ring containing from 6 to 9 carbon atoms and the nitrogen bearing R^3 include

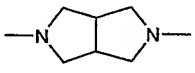




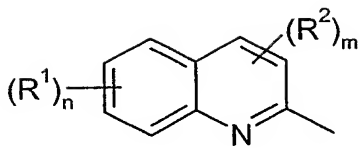
Examples where the group –L^1-N(R^4)- together represents a heterocyclic ring containing from 2 to 9 carbon atoms and the nitrogen bearing R^4 include:



Examples where the group –N(R^3)-L^1-N(R^4)- together represents a heterocyclic ring containing from 6 to 8 carbon atoms and the two nitrogens bearing R^3 and R^4 respectively include:

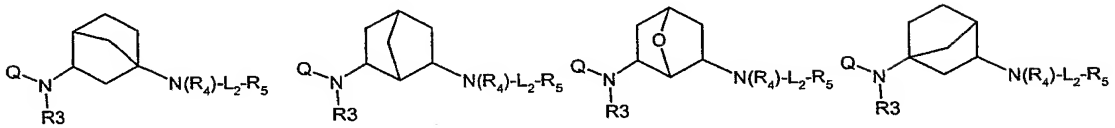


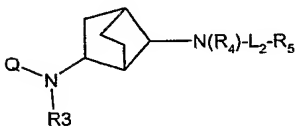
It will be understood that in the above the free bond to the left of the page is attached to the nitrogen bearing R^3 (or to the quinoline ring) and the free bond to the right of the page is attached to the nitrogen bearing R^4 (or to L2). For the avoidance of doubt when Q represents



Q

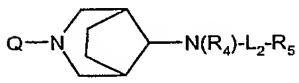
Examples of compounds where L^1 is bicyclic include

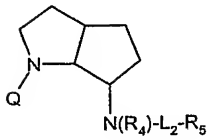




in which Q, R^3, R^4, L^2 and R^5 are as previously defined.

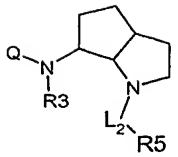
Examples of compounds where $-N(R^3)-L^1-$ together represents a saturated heterocyclic ring containing from 6 to 9 carbon atoms and the nitrogen bearing R^3 include





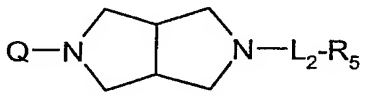
in which Q, R^3, R^4, L^2 and R^5 are as previously defined.

Examples of compounds where $-L^1-N(R^4)-$ together represent a saturated heterocyclic ring containing from 6 to 9 carbon atoms and the nitrogen bearing R^4 include compounds of formula



in which Q, R^3, R^4, L^2 and R^5 are as previously defined.

Examples of compounds where the group $-N(R^3)-L^1-N(R^4)-$ together represents a heterocyclic ring containing from 6 to 8 carbon atoms and the two nitrogens bearing R^3 and R^4 respectively, include compounds of formula:



in which Q, L^2 and R^5 are as previously defined.

Further particular values of R^1, R^2, R^3, R^4, R^5, L^1, L^2, n and m in compounds of formula I now follow. It will be understood that such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

Particularly R^1 represents H, methoxy, fluoro, chloro or dimethylamino.
Particularly R^2 represents H, methyl, methoxy, dimethylamino or *N,N*-dimethylcarbamoyl.
Particularly R^5 represents one of the following : 3-thienyl, 1-methylpyrrol-2-yl, 1-methylindol-3-yl, 2,4-dimethoxypyrimidin-5-yl, 2-(phenylsulfonyl)-1,3-thiazol-5-yl, 1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]-2-thienyl, 1-[(2-chloro-1,3-thiazol-5-yl)methyl]-1*H*-indol-3-yl}, 5-(2-thienyl)thien-2-yl, 5-pyridin-2-yl-2-thienyl, 1,2,3-thiadiazol-4-yl, 4-chloro-1-methyl-1*H*-pyrazol-3-yl and quinolin-2-yl.

In one particular group of compounds of formula I B, R^1 represents H, methoxy, fluoro, chloro or dimethylamino; R^2 represents H, methyl, methoxy, dimethylamino or *N,N*-dimethylcarbamoyl, L^2 represents CH_2, A is CH_2 , t is 0 or 1; R^3 and R^4 are each H, and R^5 is 3-thienyl, 1-methylpyrrol-2-yl, 1-methylindol-3-yl, 2,4-dimethoxypyrimidin-5-yl, 2-(phenylsulfonyl)-1,3-thiazol-5-yl, 1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]-2-

thienyl, 1-[(2-chloro-1,3-thiazol-5-yl)methyl]-1*H*-indol-3-yl}, 5-(2-thienyl)thien-2-yl, 5-pyridin-2-yl-2-thienyl, 1,2,3-thiadiazol-4-yl, 4-chloro-1-methyl-1*H*-pyrazol-3-yl and quinolin-2-yl.

In another particular group of compounds of formula I B, R^1 represents fluoro, chloro or dimethylamino; R^2 represents H, methyl, methoxy, dimethylamino or *N,N*-dimethylcarbamoyl, L^2 represents CH_2, A is CH_2 , t is 0 or 1; R^3 and R^4 are each H, and R^5 is 3-thienyl, 1-methylpyrrol-2-yl, 1-methylindol-3-yl, 2,4-dimethoxypyrimidin-5-yl, 2-(phenylsulfonyl)-1,3-thiazol-5-yl, 1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]-2-thienyl, 1-[(2-chloro-1,3-thiazol-5-yl)methyl]-1*H*-indol-3-yl}, 5-(2-thienyl)thien-2-yl, 5-pyridin-2-yl-2-thienyl, 1,2,3-thiadiazol-4-yl, 4-chloro-1-methyl-1*H*-pyrazol-3-yl and quinolin-2-yl.

The term "pharmaceutically acceptable salt", where such salts are possible, includes both pharmaceutically acceptable acid and base addition salts. A suitable pharmaceutically acceptable salt of a compound of Formula **I** is, for example, an acid-addition salt of a compound of Formula **I** which is sufficiently basic, for example an acid-addition salt with an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric, trifluoroacetic, citric or maleic acid; or, for example a salt of a compound of Formula I which is sufficiently acidic, for example an alkali or alkaline earth metal salt such as a sodium, calcium or magnesium salt, or an ammonium salt,or a salt with an organic base such as methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

Throughout the specification and the appended claims, a given chemical formula or name shall encompass all stereo and optical isomers and racemates thereof as well as mixtures in different proportions of the separate enantiomers, where such isomers and enantiomers exist, as well as pharmaceutically acceptable salts thereof. Isomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The enantiomers may be isolated by separation of racemate for example by fractional crystallisation, resolution or HPLC. The diastereomers may be isolated by separation of

isomer mixtures for instance by fractional crystallisation, HPLC or flash chromatography. Alternatively the stereoisomers may be made by chiral synthesis from chiral starting materials under conditions which will not cause racemisation or epimerisation, or by derivatisation, with a chiral reagent. All stereoisomers are included within the scope of the invention.

The following definitions shall apply throughout the specification and the appended claims.

Unless otherwise stated or indicated, the term "alkyl" denotes either a straight or branched alkyl group. Examples of said alkyl include methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl and t-butyl . Preferred alkyl groups are methyl, ethyl, propyl, isopropyl and tertiary butyl.

Unless otherwise stated or indicated, the term "alkoxy" denotes a group O-alkyl, wherein alkyl is as defined above.

Unless otherwise stated or indicated, the term "halo" shall mean fluorine, chlorine, bromine or iodine.

Specific compounds of the invention include one or more of the following:
N,*N*-dimethyl-2-[(3-{[(5-pyridin-2-yl-2-thienyl)methyl]amino}cyclohexyl)amino]-quinoline-4-carboxamide;
(1*S*,3*S*)-*N*-(6-chloro-4-methylquinolin-2-yl)-*N*'-[(1-methyl-1*H*-indol-3-yl)methyl]cyclohexane-1,3-diamine
(1*S*,3*S*)-*N*-(6-fluoro-4-methylquinolin-2-yl)-*N*'-(3-thienylmethyl)cyclohexane-1,3-diamine
(1*R*,3*R*)-*N*-(6-fluoro-4-methylquinolin-2-yl)-*N*'-(3-thienylmethyl)cyclohexane-1,3-diamine
(1*S*,3*S*)-*N*-(6-fluoro-4-methoxyquinolin-2-yl)-*N*'-(3-thienylmethyl)cyclohexane-1,3-diamine
(1*S*,3*S*)-*N*-(6-fluoro-4-methylquinolin-2-yl)-*N*'-[(1-methyl-1*H*-indol-3-yl)methyl]cyclopentane-1,3-diamine
N-(6-chloroquinolin-2-yl)-*N*'-(3-thienylmethyl)cyclohexane-1,3-diamine

N-(6-chloroquinolin-2-yl)-*N'*-[(1-methyl-1*H*-pyrrol-2-yl)methyl]cyclohexane-1,3-diamine

N-(6-chloroquinolin-2-yl)-*N'*-(quinolin-3-ylmethyl)cyclohexane-1,3-diamine

N^6,N^6-dimethyl-N^2-{3-[(3-thienylmethyl)amino]cyclohexyl}quinoline-2,6-diamine

(1*S*,3*S*)-*N*-[(4-chloro-1-methyl-1*H*-pyrazol-3-yl)methyl]-*N'*-(6-methoxy-4-methylquinolin-2-yl)cyclopentane-1,3-diamine

(1*S*,3*S*)-*N*-(6-methoxy-4-methylquinolin-2-yl)-*N'*-(1,2,3-thiadiazol-4-ylmethyl)cyclopentane-1,3-diamine

(1*S*,3*S*)-*N*-(6-methoxy-4-methylquinolin-2-yl)-*N'*-[(5-pyridin-2-yl-2-thienyl)methyl]cyclopentane-1,3-diamine

(1*S*,3*S*)-*N*-({1-[(2-chloro-1,3-thiazol-5-yl)methyl]-1*H*-indol-3-yl}methyl)-*N'*-(6-methoxy-4-methylquinolin-2-yl)cyclopentane-1,3-diamine

(1*S*,3S)-*N*-(6-methoxy-4-methylquinolin-2-yl)-*N'*-({5-[1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]-2-thienyl}methyl)cyclopentane-1,3-diamine

(1*S*,3*S*)-*N*-(2,2'-bithien-5-ylmethyl)-*N'*-(6-methoxy-4-methylquinolin-2-yl)cyclopentane-1,3-diamine

N^4,N^4-dimethyl-N^2-{3-[(3-thienylmethyl)amino]cyclohexyl}quinoline-2,4-diamine

N^4,N^4-dimethyl-N^2-[3-({[2-(phenylsulfonyl)-1,3-thiazol-5-yl]methyl}amino)-cyclohexyl]quinoline-2,4-diamine

N^2-(3-{[(2,4-dimethoxypyrimidin-5-yl)methyl]amino}cyclohexyl)-N^4,N^4-dimethylquinoline-2,4-diamine

3-(6-Methoxy-4-methylquinolin-2-yl)-N-methyl-N-(3-thienylmethyl)-3-azabicyclo[3.2.1]octan-8-amine

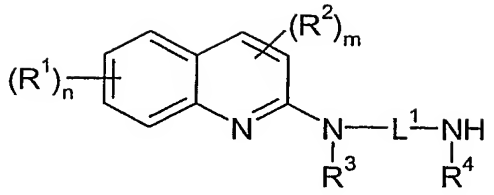
6-Methoxy-4-methyl-2-[5-(3-thienylmethyl)hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl]quinoline

and pharmaceutically acceptable salts thereof.

Methods of preparation

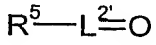
The compounds of the invention may be prepared as outlined below according to any of the following methods. However, the invention is not limited to these methods, the compounds may also be prepared as described for structurally related compounds in the prior art.

Compounds of formula I may be prepared by reacting a compound of formula II



II

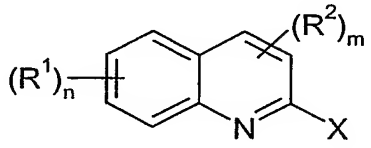
in which R^1, R^2, R^3, R^4, L^1, n and m are as previously defined with an aldehyde or a ketone of formula III



III

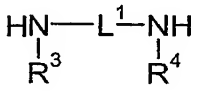
in which R^5 is as previously defined and $L^{2'}$ represents a group which after reaction of compounds II and III gives L^2 on reduction, under reductive alkylation conditions. For example, a compound of formula II and a compound of formula III may be reacted together at a temperature in the range of 0°C to 250°C, preferably in the range of 50°C to 150°C, optionally in the presence of an inert solvent, for example methanol, dichloromethane or acetic acid in the presence of a reducing agent, for example sodium cyanoborohydride or optionally polymer supported cyanoborohydride.

Compounds of formula II may be prepared by reacting a compound of formula IV



IV

in which R^1, R^2, n and m are as previously defined and X is halo, particularly chloro or bromo, with a compound of formula V

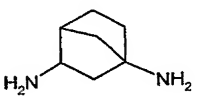


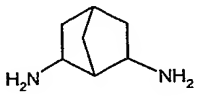
V

at a temperature in the range of 0°C to 250°C, preferably in the range of 50°C to 150°C in pyridine or optionally in the presence of an inert solvent, for example toluene or dioxane in the presence of a catalytic cross-coupling system for example $Pd(OAc)_2$ and 2-(di-^{t}butylphosphino)biphenyl or BINAP, and optionally in the presence of a base for example NaO^tBu or Cs_2CO_3.

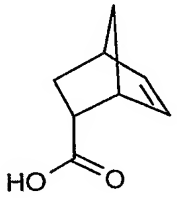
Certain compounds of formula II and V are novel and are claimed as a further aspect of the present invention as useful intermediates.

Compounds of formula V, in which L^1 represents a bicyclic ring, for example:

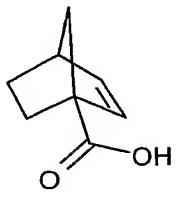




may be prepared e.g. starting from X (T., Poll; *Tetrahedron Letters*, 1989, 30,41, 5595-5598) or XI (G.L., Grunewald; *J.Org.Chem.* 1978, 43, 15, 3074-3076), utilizing standard techniques, e.g. Curtius rearangement and hydroboration, for conversion of carboxylic acids and olefins into amines.

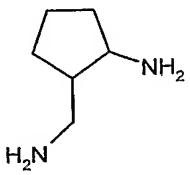


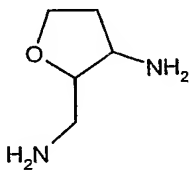
X



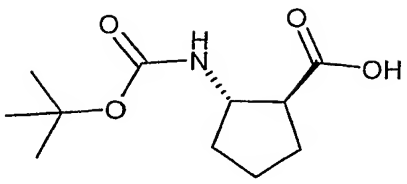
XI

Compounds of formula V, in which L^1 represents a cyclopentylmethyl or tetrahydrofuryl-methyl, for example:





may be prepared e.g. as outlined in *Bioorg.Med.Chem.Lett.* 13, 1265-68 (2003), and references cited therein, or, alternatively, by conversion of compound XII into a diamine by standard transformations (e.g reduction of the acid to alcohol followed by conversion to amine via substitution of the corresponding sulfonate with azide followed by reduction).



XII

Optionally one or both nitrogens in formula V may be protected prior to reaction with a compound of formula IV and then the compound of formula II obtained is deprotected prior to reaction with a compound of formula III. Amine protecting groups are known to those skilled in the art for example the t-Boc, Cbz or phtalimido groups.
The compounds of the invention may be isolated from their reaction mixtures using conventional techniques.

Persons skilled in the art will appreciate that, in order to obtain compounds of the invention in an alternative and in some occasions, more convenient manner, the individual process steps mentioned hereinbefore may be performed in a different order, and/or the individual reactions may be performed at a different stage in the overall route (i.e. chemical transformations may be performed upon different intermediates to those associated hereinbefore with a particular reaction).

The expression "inert solvent" refers to a solvent which does not react with the starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product.

Pharmaceutical preparations

The compounds of the invention will normally be administered via the oral, parenteral, intravenous, intramuscular, subcutaneous or in other injectable ways, buccal, rectal, vaginal, transdermal and/or nasal route and/or via inhalation, in the form of pharmaceutical preparations comprising the active ingredient either as a free acid, or a pharmaceutically acceptable organic or inorganic base addition salt, in a pharmaceutically acceptable dosage

form. Depending upon the disorder and patient to be treated and the route of administration, the compositions may be administered at varying doses.

Suitable daily doses of the compounds of the invention in the therapeutic treatment of humans are about 0.001-10 mg/kg body weight, preferably 0.01-1 mg/kg body weight.

Oral formulations are preferred particularly tablets or capsules which may be formulated by methods known to those skilled in the art to provide doses of the active compound in the range of 0.5mg to 500mg for example 1 mg, 3 mg, 5 mg, 10 mg, 25mg, 50mg, 100mg and 250mg.

According to a further aspect of the invention there is also provided a pharmaceutical formulation including any of the compounds of the invention, or pharmaceutically acceptable derivatives thereof, in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

The compounds of the invention may also be combined with other therapeutic agents which are useful in the treatment of disorders associated with obesity, psychiatric disorders, neurological disorders and pain.

Pharmacological properties

The compounds of formula (I) are useful for the treatment of obesity, psychiatric disorders such as psychotic disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, schizophrenia, epilepsy, and related conditions, and neurological disorders such as dementia, multiple sclerosis, Raynaud's syndrome , Parkinson's disease, Huntington's chorea and Alzheimer's disease. The compounds are also potentially useful for the treatment of immune, cardiovascular, reproductive and endocrine disorders, and diseases related to the respiratory and gastrointestinal systems. The compounds are also potentially useful as agents for ceasing consumption of tobacco, treating nicotine dependence and/or treating nicotine withdrawal symptoms, reducing the craving for nicotine and as anti-smoking agents. The compounds may also eliminate the

increase in weight that normally accompanies the cessation of smoking. The compounds are also potentially useful as agents for treating or preventing diarrhoea.

The compounds are also potentially useful as agents for reducing the craving/relapse for addictive substances that include, but are not limited to psychomotor-active agents such as nicotine, alcohol, cocaine, amphetamines, opiates, benzodiazepines and barbiturates. The compounds are also potentially useful as agents for treating drug addiction and/or drug abuse.

Accordingly, it is desirable to provide a compound and method of treatment which will be active in reducing craving for the abused substance, and which does not exacerbate the sympathetic response rate caused by the abused substance and which has favorable pharmacodynamic effects.

The compounds are also potentially useful as agents for treating pain disorders , including but not limited to acute and chronic nociceptive, inflammatory and neuropathic pain and migraine.

In another aspect the present invention provides a compound of formula I as claimed in any previous claim for use as a medicament.

In a further aspect the present invention provides the use of a compound of formula I in the preparation of a medicament for the treatment or prophylaxis of obesity, psychiatric disorders such as psychotic disorders, anxiety, anxio-depressive disorders, depression, bipolar disorder, ADHD, cognitive disorders, memory disorders, schizophrenia, epilepsy, and related conditions, neurological disorders such as dementia, multiple sclerosis, Parkinson's disease, Huntington's chorea and Alzheimer's disease and pain related disorders , including but not limited to acute and chronic nociceptive, inflammatory and neuropathic pain and migraine, comprising administering a pharmacologically effective amount of a compound of formula I to a patient in need thereof.

In a still further aspect the present invention provides a method of treating obesity, psychiatric disorders such as psychotic disorders, anxiety, anxio-depressive disorders, depression, bipolar disorder, ADHD, cognitive disorders, memory disorders, schizophrenia, epilepsy, and related conditions, and neurological disorders such as dementia, multiple sclerosis, Parkinson's disease, Huntington's chorea and Alzheimer's disease and pain related disorders, including but not limited to acute and chronic nociceptive, inflammatory and neuropathic pain and migraine, comprising administering a pharmacologically effective amount of a compound of formula I to a patient in need thereof.

The compounds of the present invention are particulary suitable for the treatment of obesity.

In another aspect the present invention provides a method of treating obesity, type II diabetes, Metabolic syndrome and a method of preventing type II diabetes comprising administering a pharmacologically effective amount of a compound of formula I to a patient in need thereof.

Combination Therapy

The compounds of the invention may be combined with another therapeutic agent that is useful in the treatment of disorders associated with the development and progress of atherosclerosis such as hypertension, hyperlipidaemias, dyslipidaemias, diabetes and obesity. For example, a compound of the present invention may be used in combination with a compound that affects thermogenesis, lipolysis, fat absortion, satiety, or gut motility. The compounds of the invention may be combined with another therapeutic agent that decreases the ratio of LDL:HDL or an agent that causes a decrease in circulating levels of LDL-cholesterol. In patients with diabetes mellitus the compounds of the invention may also be combined with therapeutic agents used to treat complications related to micro-angiopathies.

The compounds of the invention may be used alongside other therapies for the treatment of metabolic syndrome or type 2 diabetes and its associated complications, these include biguanide drugs, insulin (synthetic insulin analogues) and oral antihyperglycemics (these

are divided into prandial glucose regulators and alpha-glucosidase inhibitors).

In another aspect of the invention, the compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, may be administered in association with a PPAR modulating agent. PPAR modulating agents include but are not limited to a PPAR alpha and/or gamma agonist, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Suitable PPAR alpha and/or gamma agonists, pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof are well known in the art.

In addition the combination of the invention may be used in conjunction with a sulfonylurea. The present invention also includes a compound of the present invention in combination with a cholesterol-lowering agent. The cholesterol-lowering agents referred to in this application include but are not limited to inhibitors of HMG-CoA reductase (3-hydroxy-3-methylglutaryl coenzyme A reductase). Suitably the HMG-CoA reductase inhibitor is a statin

In the present application, the term "cholesterol-lowering agent" also includes chemical modifications of the HMG-CoA reductase inhibitors, such as esters, prodrugs and metabolites, whether active or inactive.

The present invention also includes a compound of the present invention in combination with an inhibitor of the ileal bile acid transport system (IBAT inhibitor). The present invention also includes a compound of the present invention in combination with a bile acid binding resin.

According to an additional further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration one or more of the following agents selected from:

a CETP (cholesteryl ester transfer protein) inhibitor;

a cholesterol absorption antagonist;

a MTP (microsomal transfer protein) inhibitor ;

a nicotinic acid derivative, including slow release and combination products;

a phytosterol compound ;

probucol;

an anti-obesity compound for example orlistat (EP 129,748) and sibutramine (GB 2,184,122 and US 4,929,629);

an antihypertensive compound for example an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, an andrenergic blocker, an alpha andrenergic blocker, a beta andrenergic blocker, a mixed alpha/beta andrenergic blocker, an andrenergic stimulant, calcium channel blocker, an AT-1 blocker, a saluretic, a diuretic or a vasodilator;

a CB1 antagonist or inverse agonist ;

another Melanin concentrating hormone (MCH) antagonist;

a PDK inhibitor; or

modulators of nuclear receptors for example LXR, FXR, RXR, and RORalpha;

an SSRI;

a serotonin antagonist;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

Therefore in an additional feature of the invention, there is provided a method for for the treatment of type 2 diabetes and its associated complications in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of a compound from one of the other classes of compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in an additional feature of the invention, there is provided a method of treating hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the present invention there is provided a kit comprising a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the present invention there is provided a kit comprising:
a) a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a first unit dosage form;
b) a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof; in a second unit dosage form; and
c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:

a) a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;

b) a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

According to another feature of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the the treatment of metabolic syndrome or type 2 diabetes and its associated complications in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

Working examples

The invention will now be described in more detail with the following examples that are not to be construed as limiting the invention.

Abbreviations

aq.	aqueous
Ac	acetyl
BINAP	*rac*-2,2'-Bis(diphenyl-phosphino)-1,1'-binaphtyl
Bu	butyl
DCM	dichloromethane
DMF	*N,N*-dimethylformamide
ELS	evaporative light scattering
Et	ethyl
HEK	human embryotic kidney
HPLC	high performance liquid chromatography
LC	liquid chromatography
MS	mass spectroscopy
Pol-BH_3CN	(polystyrylmethyl)trimethylammonium cyanoborohydride (loading 4.1-4.3 mmol BH_3CN/g)
Pol-CHO	4-benzyloxybenzaldehyde polystyrene (loading ~2.66 mmol CHO/g)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
Tris	trishydroxymethylaminomethane
t	tert
rt.	room temperature
sat.	saturated
br	broad
bs	broad singlet
bt	broad triplet
d	doublet

dd	doublet of doublets
m	multiplet
q	quartet
s	singlet
t	triplet
tt	triplet of triplets
td	triplet of doublets
bd	broad doublet

General Experimental Procedures

Flash column chromatography employed MERCK normal phase silica gel 60 Å (40-63 µm) or a Biotage Horizon Pioneer® HPFC system equipped with FLASH 12+M or FLASH 25+M or 40+M silica cartridges. Mass spectra were recorded on a Waters Micromass ZQ single quadrupole equipped with a pneumatically assisted electrospray interface (LC-MS). Purifications were performed on a Waters Prep LC 2000 with UV-detection, equipped with a Kromasil 10 µm C8 250 mm x 20 mm column, or on a semi preparative HPLC, Shimadzu LC-8A, Shimadzu SPD-10A UV-vis.-detector equipped with a Waters Symmetry® 100 mm x 19 mm C18 5 µm column.

Automated HPLC purification was done using a Waters Fraction Lynx system equipped with UV, ELS and MS detection and an Ace C8 5µ 10 cm x 21,2 id column. The mobile phase was A: 95% CH_3CN and B: 5% CH_3CN + 95% 0,1 M NH_4OAc with a gradient from 100% B to 100% A in 10 minutes at 25 mL/min flow rate.

^1H NMR and ^{13}C NMR spectra were obtained at 298 K on a Varian Unity Plus 400 mHz, or a Varian Inova 500 MHz or a Varian Unity Plus 600 MHz or a Bruker Avance 300 MHz. Chemical shifts are given in ppm with the solvent residual peak as internal standard: $CDCl_3$ δ_H 7.26, δ_C 77.2; MeOH-d_4 δ_H 3.31, δ_C 49.0; DMSO-d_6 δ_H 2.50; δ_C 39.5 ppm. Microwave heating was performed using single node heating in a Smith Creator from Personal Chemistry, Uppsala, Sweden.

Analytical chiral HPLC was done using a Chiralcel OJ (250x4.6 mm i.d.) column with EtOH:Et_3N 100:0.1 as mobile phase at flow rate 1 mL/min and with UV detection at 254 or 350 nm.

Names/reference numbers of starting materials **(CAS no)**, either commercially available or prepared by published methods.

cyclohexane-1,3-diamine, 3385-21-5; 2,4-dichloroquinoline, 703-61-7; (–)-2-azabicyclo[2.2.1]hept-5-en-3-one, 79200-56-9; 1-methylindole-3-carbaldehyde, 19012-03-4; 2-chloro-6-methoxy-4-methylquinoline. 6340-55-2; 4-fluoroaniline, 371-40-4; 3-thiophenecarbaldehyde, 498-62-4; 5381-20-4; *rac*-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), 98327-87-8; 2-chloroquinoline-4-carboxylic acid, 5467-57-2; 2,6-dichloroquinoline,151703-14-9; 2-chloro-6-fluoro-4-methylquinoline, 18529-12-9; 2,2'-bithiophene-5-carbaldehyde, 3779-27-9; 2,6-dichloro-4-methylquinoline, 90723-71-0; 1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]-2-thiophene-2-carbaldehyde, 175202-93-4; (2-chloro-1,3-thiazol-5-yl)methyl-1*H*-indole-3-carbaldehyde, 439095-43-9; 1,2,3-thiadiazol-4-carbaldehyde, 27643-15-8; 4-chloro-1-methyl-1*H*-pyrazole-3-carbaldehyde, 175204-81-6; quinoline-3-carbaldehyde, 13669-42-6; 1-methylpyrrole-2-carbaldehyde, 406695-47-4; 5-pyridin-2-ylthiophene-2-carbaldehyde, 132706-12-8; 2-(phenylsulfonyl)-1,3-thiazole-5-carbaldehyde, 477886-95-6; 2,4-dimethoxypyrimidine-5-carbaldehyde, 52606-02-7; 5-pyridine-2-yl-thiophene-2-carbaldehyde 13270-12-8.

Preparation of Intermediates

***Tert*-butyl [(1*S*,3*S*)-3-aminocyclopentyl]carbamate**

a) (1*R*,3*S*)-3-[(*tert*-butoxycarbonyl)amino]cyclopentyl methanesulfonate

Prepared according to WO9811103 from (–)-2-azabicyclo[2.2.1]hept-5-en-3-one (>95% ee).

b) *Tert*-butyl [(1*S*,3*S*)-3-azidocyclopentyl]carbamate

NaN_3 (16.6 g, 0.25 mmol) was added to a stirred solution of (1*R*,3*S*)-3-[(*tert*-butoxycarbonyl)amino]cyclopentyl methanesulfonate (20 g, crude, ~0.05 mol) in DMF (250 mL) under nitrogen atmosphere. The mixture was heated to 50 °C for 18 h (over night). The mixture was allowed to reach rt., poured into H_2O (200 mL), extracted with EtOAc (2 × 400 mL), 200 mL Et_2O and concentrated. Purification of the residue by flash chromatography [280 g silica gel, 6 × 22 cm column, with EtOAc/heptane (2:3 → 1:1) as eluent] afforded the title compound (16.5 g, contaminated with DMF) as a slightly yellowish oil taken to the next step without further purification.

^{1}H NMR (300.1 MHz, $CDCl_3$) δ 4.52 (bs , 1H), 4.00–4.10 (m, 2H), 1.98–2.22 (m, 3H), 1.62–1.78 (m, 2H), 1.42–1.52 (m, 1H), 1.44 (s, 9 H).

c) *Tert*-butyl [(1*S*,3*S*)-3-aminocyclopentyl]carbamate

A flask containing *tert*-butyl [(1*S*,3*S*)-3-aminocyclopentyl]carbamate (16.5 g, crude ~0.05 mol) and 1.7 g Pd-C (10% paste) in MeOH (300 mL) was exposed to a positive pressure of hydrogen gas (balloon) over weekend. The catalyst was filtered off and the mixture was concentrated to afford the title compound (9.5 g) as a thick colorless viscous oil.

^{1}H NMR (300.1 MHz, DMSO-d_6) δ 6,74 (bd , 1H), 3.86–3.92 (m, 1H), 3.28 (quintet, 1H), 1.73–1.98 (m, 2H), 1.43–1.59 (m, 2H), 1.22–1.41 (m, 1H), 1.36 (s, 9 H), 1.07–1.20 (m, 1H).

^{13}C NMR (DMSO-d_6) δ 155.0, 77.2, 50.8, 50.0, 42.6, 34.2, 31.2, 28.3.

LC-MS $[M+H]^+$ 201

(1*S*,3*S*)-*N*-(6-methoxy-4-methylquinolin-2-yl)cyclopentane-1,3-diamine

a) *Tert*-butyl {(1*S*,3*S*)-3-[(6-methoxy-4-methylquinolin-2-yl)amino]cyclopentyl}carbamate

A mixture of 2-chloro-6-methoxy-4-methylquinoline (0.690 g, 3.33 mmol), *tert*-butyl [(1*S*,3*S*)-3-aminocyclopentyl]carbamate (1.00 g, 5.0 mmol), NaO^{t}Bu (4.66 mmol, 0.45 g), $Pd(OAc)_2$ (0.075 g, 0.33 mmol), and BINAP (0.207 g, 0.33 mmol) in toluene (30 mL) was stirred at 100 °C under nitrogen until LC-MS indicated that starting material was consumed. The reaction mixture was cooled to room temperature, poured into Et_2O (300 mL) and washed with brine. The organic layer was then separated, dried over Na_2SO_4 and evaporated to dryness. The residue was purified on a SiO_2 column eluted with DCM:MeOH (95:5) to give 0.618 g (50%) of the title compound.

b) (1*S*,3*S*)-*N*-(6-methoxy-4-methylquinolin-2-yl)cyclopentane-1,3-diamine

Tert-butyl {(1*S*,3*S*)-3-[(6-methoxy-4-methylquinolin-2-yl)amino]cyclopentyl}carbamate (0.550 g, 1.48 mmol) and TFA (3 mL) in $CHCl_3$ (7 mL) was stirred at rt. for 6 hours. LC indicated that starting material was consumed. The mixture was then evaporated to dryness. pH was set to 10 with a 2 *N* NaOH solution and then extracted with EtOAc. The

organic layer was separated, dried on $MgSO_4$ and concentrated, to give 0.400 g (99%) of the title compound.

^{1}H NMR (300.1 MHz, $CDCl_3$) δ 7.57 (d, 1H), 7.16-7.20 (dd 1H), 7.04 (d, 1H), 6.51 (s, 1H), 5.24 (br, 1H), 4.44 (m, 1H), 3.86 (s, 3H), 3.50 (m, 1H), 2.73 (br, 2H), 2.51 (s, 3H), 2.26 (m, 2H), 2.06 (m, 1H), 1.85 (m, 1H), 1.41 (m, 2H).

LC-MS $[M+H]^+$ 272

2-Chloro-*N*,*N*-dimethylquinolin-4-amine

Prepared from 2, 4-dichloroquinoline according to literature procedure: T. Watanabe, et al; Synthesis 1980, pp 39-41.

^{1}H NMR (300.1 MHz, DMSO-d_6) δ8.01 (d, 1H), 7.98 (d, 1H), 7.62 (dd, 1H), 7.43 (dd, 1H), 6.70 (s, 1H), 3.05 (s, 6H).

LC-MS $[M+H]^+$ 207

2-Chloro-*N*,*N*-dimethylquinolin-6-amine

a) 1-Methyl-6-nitroquinolin-2(1*H*)-one

Prepared by a modification of the procedure described by H. von Balli and D. Schelz, *Helv. Chim. Acta*, Vol. 53 (1970) pp 1903-1912, using 15 M HNO_3 and rt. as reaction temperature instead of what is written. ^{1}H NMR (300.1 MHz, DMSO-d_6) δ in agreement with those described by: N. Nishiwaki et al. *Tetrahedron*, Vol. 58 (2002) pp 473-478.

b) 2-Chloro-6-nitroquinoline

Prepared according to the procedure described by H. von Balli and D. Schelz, *Helv. Chim. Acta*, Vol. 53 (1970) pp 1903-1912.

c) 2-Chloroquinoline-6-amine

$SnCl_2 \cdot 2\ H_2O$ (42 g, 0.19 mol) was added to a stirred solution of 2-chloro-6-nitroquinoline (8.1 g, 39 mmol) in EtOH (250 mL). The mixture was refluxed for 0.5 h, cooled to rt., concentrated and dissolved in DCM (200 mL), added NaOH (150 mL, aq., 5 M) filtered and rinsed with H_2O (150 mL) followed by Et_2O (100 mL). The organic phase was washed

with $NaHCO_3$ (100 mL, aq., sat.) and concentrated, which afforded the title compound (4.9 g, 70%) as an orange-yellow, solid material, used in next step without further purification.
^1H NMR (300.1 MHz, DMSO-d_6) δ 8.01 (d, 1H), 7.62 (d, 1H), 7.30 (d, 1H), 7.19 (dd, 1H), 6.83 (d, 1H), 5.73 (s, 2H).
LC-MS $[M+H]^+$ 179

d) 2-Chloro-*N*,*N*-dimethylquinolin-6-amine

MeI (2.8 g, 20 mmol) was added to a stirred solution of 2-chloroquinoline-6-amine (4.7 g, 25 mmol) and K_2CO_3 (3.6 g, 26 mmol) in DMF (300 mL) under nitrogen atmosphere. The mixture was heated to 70 °C for 0.5 h and additional MeI (0.9 g, 6 mmol) was then added, and then stirred for 5 h. The mixture was allowed to reach rt. and poured into H_2O (200 mL) and extracted with DCM (2 × 200 mL) and concentrated. Purification of the residue by flash chromatography [120 g silica gel, 6 × 9 cm column, with EtOAc/heptane (2:3 → 3:2) followed by DCM:MeOH (95:5 + 1% Et_3N) as eluent] afforded a mixture of mono- and di-N-methylated compounds (0.9 g) as an yellow solid material. The unreacted 2-chloroquinoline-6-amine isolated (2.8 g) was reacted again in the same manner as described above (1.7 g + 0.7 g MeI, 2.3 g K_2CO_3, 175 mL DMF) to give an additional 1.7 g of product mixture. The combined batches were purified by flash chromatography (SiO_2, Heptane:EtOAc) to yield 0.91 g of the title compound.
^1H NMR (300.1 MHz, DMSO-d_6) δ 8.15 (d, 1H), 7.75 (d, 1H), 7.48 (dd, 1 H), 7.38 (d, 1H), 6.99 (d, 1H), 3.04 (s, 3H), 3.02 (s, 3H).
LC-MS $[M+H]^+$ 207

Dibenzyl *trans*-cyclohexane-1,3-diylbiscarbamate

D-tartaric acid (15.77 g, 105 mmol) was added to a stirred solution of cyclohexane-1,3-diamine (12 g, 105 mmol, cis/trans ~2.6:1) in H_2O (80 mL). The resulting mixture was heated to ~60 °C and MeOH (800 mL) was slowly added. The mixture was allowed to attain rt and left for 3 days. The precipitate was filtered off and the filtrate was concentrated and redissolved in 1M NaOH (40 mL). To the stirred mixture at 0 °C was added benzyl chloroformate (9.56 g, 56 mmol) and 1M NaOH (40 mL). After 5 min, 1,4-dioxane (40 mL) was added and the mixture stirred for an additional 18 h at rt. The mixture was diluted with H_2O and extracted with CH_2Cl_2. The organic layer was dried with

$MgSO_4$, filtered and concentrated. Purification on a Biotage Horizon 40+M SiO_2 column gave 5.61 g (14%) of the title compound as a white solid.

^1H NMR (400 MHz, MeOH-d_4) δ 7.36-7.26 (m, 5H), 5.06 (bs, 2H), 3.77 (b, 2H), 1.73-1.42 (m, 8H).

LC-MS $[M+H]^+$ 383.4

(+) Dibenzyl-*trans*-cyclohexane-1,3-diylbiscarbamate

The enantiomers of dibenzyl-*trans*-cyclohexane-1,3-diylbiscarbamate were separated by preparative chiral chromatography. 7.27 g were dissolved in EtOH (56 mg/mL), repeated 2 mL (112 mg) injections on a Chiralcel OJ (250 x 20 mm i.d.), eluted with EtOH:Et_3N 100/0.1, 12 mL/min, gave 3.75 g of the title compound, 99.3% ee, $[\alpha]^{20}_D$ +2.7 (c 1.26, MeOH) and 2.45 g of (-)dibenzyl-*trans*-cyclohexane-1,3-diylbiscarbamate, 83% ee.

(1*S*, 3*S*)-Cyclohexane-1,3-diamine dihydrochloride

(+)dibenzyl-*trans*-cyclohexane-1,3-diylbiscarbamate (0.24 mmol, 0.090g) and 10% Pd on activated carbon (0.010 g) in EtOH (5mL) was stirred under a H_2-atmosphere. After 1 h, the mixture was filtered through Celite and concentrated to give 44 mg of the title compound (100%). The product was recrystallized from MeOH/Et_2O and the absolute configuration was determined by X-ray crystallography.

2-Chloro-6-fluoro-4-methoxyquinoline

a) 2,4-Dichloro-6-fluoro-quinoline

To a mixture of 4-fluoroaniline (8.5 g, 76.5 mmol) and malonic acid (8.0 g, 76.9 mmol) was added $POCl_3$ (160 g, 1.04 mol) and the mixture was slowly heated to 100°C and then kept at this temperature for 18 h. The reaction mixture was cooled to room temperature and poured into ice-water (1.0 L). The brown slurry was filtered and the solid brown/orange material was purified by flash chromatography [350 g SiO_2, 6 × 24 cm column, eluting with DCM], which afforded 3.37 g (20%) of the title compound as an off-white solid.

b) 2-Chloro-6-fluoro-4-methoxy-quinoline

To 2,4-dichloro-6-fluoro-quinoline (3.3 g, 15 mmol) in MeOH (50 mL) was added NaOMe (2.5 g, 46 mmol) at rt. under an atmosphere of nitrogen. The slurry was heated at reflux for

2 h, cooled to rt. and concentrated. The residue was purified by flash chromatography [60 g SiO_2, 4 × 12 cm column, eluting with DCM], which afforded 2.17 g (69%) of the title compound as a white solid material.

^{1}H NMR (300.1 MHz, $CDCl_3$) δ 7.89 (dd, 1H), 7.68 (dd, 1H), 7.43 (ddd, 1H), 6.71 (s, 1H), 4.02 (s, 3H).

LC-MS $[M+H]^+$ 212

Examples

Example 1

***N*,*N*-dimethyl-2-[(3-{[(5-pyridin-2-yl-2-thienyl)methyl]amino}cyclohexyl)amino]quinoline-4-carboxamide**

a) 2-Chloroquinoline-4-carbonyl chloride

2-chloroquinoline-4-carboxylic acid (0.5 g, 2.4 mmol) was slurried in 5 mL of DCM. Oxalyl chloride (0.41 mL, 4.8 mmol) was added and the reaction was started by the addition of two drops of DMF. The reaction mixture was stirred at room temperature over night. The solvent was evaporated to yield a brown solid (0.575 g) which was used without further purification.

b) 2-Chloro-*N*,*N*-dimethylquinoline-4-carboxamide

2-chloroquinoline-4-carbonyl chloride (4.4 g, 19.5 mmol) was added to an ice-cold solution of dimethyl amine hydrochloride (1.6 g, 19.5 mmol) in Et_3N (5.4 mL) and DCM (46 mL). The ice bath was removed and the reaction mixture was stirred at room temp for 2.5 h and was then diluted with 150 mL of DCM. After washing with water and brine, the solution was dried over Na_2SO_4, filtered and evaporated. Flash chromatography (SiO_2, EtOAc) gave a brownish, solid compound (4.2 g, 91%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, 1H), 7.70-7.77 (m, 2H), 7.57 (m, 1H), 7.30 (s, 1H), 3.22 (s, 3H), 2.82 (s, 3H).

LC-MS $[M+H]^+$ 234.9, 236.8.

c) 2-[(3-Aminocyclohexyl)amino]-*N*,*N*-dimethylquinoline-4-carboxamide

2-chloro-*N*,*N*-dimethylquinoline-4-carboxamide (0.42 g, 1.79 mmol) and cyclohexane-1,3-diamine (0.82 g, 7.2 mmol) were dissolved in pyridine (4 mL) and the solution was heated in a microwave oven at 175 °C for 20 minutes. The solvent was removed and the residue was purified using flash chromatography (SiO_2, 5:1 EtOAc:MeOH with 1% Et_3N) to yield the title compound as a mixture of stereoisomers (171 mg, 31%).

^{1}H NMR (400 MHz, MeOH-d_4; mixture of diastereomers) δ 7.63 (d, 1H), 7.52 (m, 1H), 7.41 (m, 1H), 7.20 (m, 1H), 6.72 (s, 1H, minor), 6.62 (s, 1H, major), 4.43 (m, 1H, minor), 4.03 (m, 1H, major), 3.191 (s, 3H, minor), 3.187 (s, 3H, major), 3.09 (m, 1H, minor), 2.86 (s, 3H), 2.85 (m, 1H, major), 2.27-2.34 (m, 1H), 1.40-2.15 (m, 7H).

LC-MS $[M+H]^+$ 313.1

d) *N*,*N*-dimethyl-2-[(3-{[(5-pyridin-2-yl-2-thienyl)methyl]amino}cyclohexyl)amino]quinoline-4-carboxamide

Pol-BH_3CN (146 mg, ca 0.60 mmol) was suspended (swollen) in 0.6 mL of DCM. 2-[(3-aminocyclohexyl)amino]-*N*,*N*-dimethylquinoline-4-carboxamide (42 mg, 0.13 mmol) was dissolved in 1.2 mL of DCM:MeOH 1:1 and was mixed with a solution of 5-pyridin-2-ylthiophene-2-carbaldehyde (20 mg, 0.11 mmol) in 0.6 mL of DCM.

The combined solution was added to the polymer bound reducing agent and 0.06 mL of HOAc was added. The mixture was heated in a microwave oven at 100 °C for 10 minutes. The solution was cooled, filtered, evaporated and re-dissolved in DCM (1 mL). Aldehyde Wang resin (0.10 g, loading 2.66 mmol/g) was added and the mixture was stirred at room temperature for 24 hours. The polymer was filtered off and was washed with DCM:MeOH 1:1. The combined solutions was applied to a 1g Isolute SCX-2 ion exchange column which was washed with 10 mL of MeOH. Elution with 7 mL of 10% Et_3N in MeOH gave the crude title product, which was further purified by flash chromatography (SiO_2, DCM:MeOH 9:1) to yield the title compound as a mixture of stereoisomers (36 mg, 55%).

^{1}H NMR (400 MHz, MeOH-d_4; mixture of diastereomers) δ 8.43 (m, 1H, major), 8.40 (m, 1H, minor), 7.38.7.80 (m, 6H), 7.14-7.23 (m, 2H + 1H, minor), 7.01 (d, 1H, major), 6.90 (s, 1H, minor), 6.62 (s, 1H, major), 4.43 (m, 1H, minor), 4.00 (s, 2H, and m, 1H, major), 3.17 (s, 3H, major), 3.16 (s, 3H, minor), 2.97 (m, 1H, minor), 2.83 (s, 3H, major), 2.81 (s, 3H, minor), 2.76 (m, 1H, major), 2.40 (m, 1H), 1.40-2.10 (m, 7H).

^{13}C NMR (101 MHz, MeOH-d_4, major isomer) δ 169.6, 156.2, 152.7, 149.0, 148.4, 145.6, 143.7, 143.2, 137.3, 130.0, 127.0, 125.8, 125.1, 124.2, 122.3, 122.0, 119.1, 119.0, 110.2, 54.4, 45.6, 44.6, 38.9, 37.9, 33.7, 32.5, 31.7, 22.9.

LC-MS $[M+H]^+$ 486.2, 487.2

Example 2

(1*S*,3*S*)-*N*-(6-chloro-4-methylquinolin-2-yl)-*N'*-[(1-methyl-1*H*-indol-3-yl)methyl]cyclohexane-1,3-diamine

a) Benzyl {(1*S*,3*S*)-3-[benzyloxycarbonyl-(6-chloro-4-methylquinolin-2-yl)amino]cyclohexyl}carbamate

(1*S*,3*S*)-Dibenzyl-cyclohexane-1,3-diylbiscarbamate (406 mg, 1.00 mmol), 2,6-dichloro-4-methylquinoline (270 mg, 1.27 mmol), palladium(II)acetate (, 23 mg, 0.10 mmol), BINAP (800 mg, 1.28 mmol), Cs_2CO_3 (830 mg, 2.55 mmol) and 3.5 mL toluene was sealed under nitrogen in a vial. The mixture was heated at 70 °C for 48 h. DCM was added and the mixture was washed with water (3X50 mL). The organic phase was dried over Na_2SO_4 and evaporated. The residue was purified on a pre-packed SiO_2-column (Isolute, 50 g) eluted with DCM:EtOAc 10:2 to yield 530 mg (80%) of the title compound.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (m, 2H), 7.61 (dd, 1H), 7.38-7.21 (m, 10H), 7.11 (s, 1H), 5.18 (bd, 2H), 5.11 (bd, 2H), 4.41 (m, 1H), 4.05 (m, 1H), 2.63 (s, 3H), 2.13-1.35 (m, 8H).

b) (1*S*,3*S*)-*N*-(6-chloro-4-methylquinolin-2-yl)cyclohexane-1,3-diamine

Benzyl {(1*S*,3*S*)-3-[benzyloxycarbonyl-(6-chloro-4-methylquinolin-2-yl)amino]cyclohexyl}carbamate (530 mg, 0.85 mmol) was hydrogenated at rt and 1 atm for 6 h with 10 % Pd-C 50 % water (160 mg) in ethanol (30 mL). The catalyst was filtered off through hyflo. Since there were still 30 % starting material left, the hydrogenation was restarted with fresh catalyst (80 mg). After 3 h all starting material was consumed. The catalyst was filtered off through hyflo and the solvent was evaporated. The residue was purified on a pre-packed SiO_2-column (Isolute, 20 g) eluted with DCM:MeOH (containing 1 % NH_4OH aq) 10:1 to yield 160 mg (59 %) of the title compound.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, 1H), 7.57 (d, 1H), 7.43 (dd, 1H), 6.51 (s, 1H), 4.30 (m, 1H), 3.13 (m, 1H), 2.52 (s, 3H), 1.92-1.55 (m, 6H), 1.36-1.25 (m, 2H)

c) (1*S*,3*S*)-*N*-(6-chloro-4-methylquinolin-2-yl)-*N*'-[(1-methyl-1*H*-indol-3-yl)methyl]cyclohexane-1,3-diamine

Pol-BH_3CN (506 mg, 2.67 mmol) was suspended in 1.2 mL of DCM. (1*S*,3*S*)-*N*-(6-chloro-4-methylquinolin-2-yl)cyclohexane-1,3-diamine (160 mg, 0.55 mmol) dissolved in 3 mL of MeOH:DCM 1:2, 1-methylindole-3-carbaldehyde (70 mg, 0.44 mmol) dissolved in 1.2 mL MeOH:DCM 1:1 and 0.16 mL HOAc was added. The mixture was heated in a microwave oven at 100 °C for 10 minutes. The reaction mixture was cooled, filtered and the solvent was evaporated. The residue was first purified on a pre-packed SiO_2-column (Isolute, 20 g) eluted with DCM:MeOH (containing 1 % NH_4OH aq) 10:1. The compound was further purified on HPLC (C8-column 250x20, gradient 0.1M NH_4OAc, 5% CH_3CN to 100 % CH_3CN). After freeze-drying the pure fractions 87 mg (36%) of the title compound was obtained.

^{1}H NMR (400 MHz, MeOH-d_4) δ 7.72 (d, 1H), 7.59-7.54 (m, 2H), 7.42 (dd, 1H), 7.27 (d, 1H), 7.17 (s, 1H), 7.14 (t, 1H), 6.96 (t, 1H), 6.64 (s, 1H), 4.43 (m, 1H), 4.34 (s, 2H), 3.58 (s, 3H), 3.37 (m, 1H), 2.56 (bd, 1H), 2.45 (s, 3H), 2.12 (bd, 1H), 1.85-1.54 (m, 6H).
^{13}C NMR (101 MHz, MeOH-d_4) δ 156.5, 145.7, 144.5, 137.2, 130.8, 129,5, 127.2, 127.1, 126,8, 124,5, 122.8, 122.1, 119.8, 118.0, 113.8, 109.5, 103.7, 51.9, 45.5, 38.8, 32.2, 31.8, 29.5, 28.7, 19.3, 17.5.
LC-MS $[M+H]^+$ 433.2

Example 3 and 4

(1*S*,3*S*)-*N*-(6-fluoro-4-methylquinolin-2-yl)-*N*'-(3-thienylmethyl)cyclohexane-1,3-diamine and

(1*R*,3*R*)-*N*-(6-fluoro-4-methylquinolin-2-yl)-*N*'-(3-thienylmethyl)cyclohexane-1,3-diamine

The title compounds (435 mg) was prepared as an enantiomerically enriched mixture (~20% ee) by a method analogous to that described for Example 2 starting from dibenzyl *trans*-cyclohexane-1,3-diylbiscarbamate (~20% ee) and the enantiomers were separated on

a Chiralcel OJ column (250 x 20 mm i.d.) using MeOH:Et_3N 100:0.1 as eluent. The collected fractions containing the pure enantiomers were evaporated, solvents were removed and each residue was re-dissolved in CH_3CN/H_2O and freeze dried. The enantiomeric ratio in the starting material is maintained in the products. Thus, the absolute configuration of the major enantiomer was assumed to be (1*S*,3*S*).

(1*S*,3*S*)-*N*-(6-fluoro-4-methylquinolin-2-yl)-*N'*-(3-thienylmethyl)cyclohexane-1,3-diamine *major enantiomer* (158 mg, 99.2 %ee)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, 1H), 7.36 (dd, 1H), 7.23-7.29 (m, 2H), 7.10 (m, 1H), 7.05 (m, 1H), 6.51 (s, 1H), 4.63 (m, 1H), 4.31 (m, 1H), 3.85 (s, 2H), 2.94 (m, 1H), 2.50 (s, 3H), 1.40-1.95 (m, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 156.9, 155.9, 145.2, 144.6, 142.0, 128.5, 127.8, 125.9, 124.0, 121.6, 118.7, 118.5, 112.2, 107.9, 107.7, 52.1, 46.4, 46.2, 37.6, 32.1, 31.9, 20.1, 19.1.

LC-MS $[M+H]^+$ 370.2

$[\alpha]_D$= -130.7 ° (c 1, MeOH)

(1*R*,3*R*)-*N*-(6-fluoro-4-methylquinolin-2-yl)-*N'*-(3-thienylmethyl)cyclohexane-1,3-diamine *minor enantiomer* (101 mg, 98.4 %ee)

LC-MS $[M+H]^+$ 370.2

$[\alpha]_D$= +125.6 ° (c 1, MeOH)

Example 5

(1*S*,3*S*)-*N*-(6-fluoro-4-methoxyquinolin-2-yl)-*N'*-(3-thienylmethyl)cyclohexane-1,3-diamine

Starting from dibenzyl (1*S*,3*S*)-cyclohexane-1,3-diylbiscarbamate (described earlier) and 2-chloro-6-fluoro-4-methoxyquinoline (described earlier), the title compound (56 mg) was prepared by a method analogous to that described for Example 2.

^{1}H NMR (400 MHz, MeOH-d_4) δ 7.45-7.55 (m, 2H), 7.19-7.7.28 (m, 2H), 7.09 (m, 1H), 7.03 (m, 1H), 6.23 (s, 1H), 4.35 (m, 1H), 3.94 (s, 3H), 3.78 (s, 2H), 2.86 (m, 1H), 2.05 (m, 1H), 1.55-1.85 (m, 6H), 1.36 (m, 1H).

^{13}C NMR (101 MHz, MeOH-d_4) δ 162.1, 158.9, 158.1, 156.6, 145.5, 140.5, 127.7, 126.5, 125.4, 122.0, 118.4, 118.2, 117.9, 105.7, 105.5, 90.9, 55.0, 51.1, 45.7, 44.9, 35.9, 31.2, 30.9, 19.7.

LC-MS $[M+H]^+$ 386.2

Example 6

(1*S*,3*S*)-*N*-(6-fluoro-4-methylquinolin-2-yl)-*N*'-[(1-methyl-1*H*-indol-3-yl)methyl]cyclopentane-1,3-diamine

a) *Tert*-butyl {(1*S*,3*S*)-3-[(6-fluoro-4-methylquinolin-2-yl)amino]cyclopentyl}carbamate

A mixture of 2-chloro-6-fluoro-4-methylquinoline (0.54 g, 2.76 mmol), *tert*-butyl [(1*S*,3*S*)-3-aminocyclopentyl]carbamate (0.69 g, 3.45 mmol), Cs_2CO_3 (2.02 g, 6.21 mmol), palladium(II) acetate (43 mg, 0.193 mmol), and BINAP (0.12 g, 0.193 mmol) in dioxane (10 mL) was heated and stirred at 80°C for 5 h. The reaction mixture was cooled to room temperature, filtered through a plug of celite and the plug washed with EtOAc and MeOH. The combined filtrate was concentrated and the residue purified by flash chromatography and eluted with heptane:EtOAc 1:1. Yield: 434 mg (44%)

^{1}H NMR (400 MHz, MeOH-d_4) δ 7.59 (dd, 1H), 7.39 (dd, 1H), 7.25 (m, 1H), 6.60 (s, 1H), 4.44 (m, 1H), 4.03 (m, 1H), 2.44 (d, J = 0.8 Hz, 3H), 1.80-2.30 (m, 4H), 1.45-1.55 (m, 2H), 1.43 (s, 9H).

LC-MS $[M+H]^+$ 360.3

b) (1*S*,3*S*)-*N*-(6-fluoro-4-methylquinolin-2-yl)cyclopentane-1,3-diamine

tert-butyl {(1*S*,3*S*)-3-[(6-fluoro-4-methylquinolin-2-yl)amino]cyclopentyl}carbamate (0.434 g, 1.21 mmol) was dissolved in DCM (4.6 mL). TFA (2.3 ml) was added and the mixture was stirred at room temperature for 4h. The pH of the solution was adjusted to about 10 with 2M NaOH (aq.) and the aqeous solution was extracted with EtOAc. The combined organic phase was dried over Na_2SO_4, filtered and evaporated. The resulting product (0.39 g) was used in the subsequent step without further purification.

LC-MS $[M+H]^+$ 260.2

c) (1*S*,3*S*)-*N*-(6-fluoro-4-methylquinolin-2-yl)-*N'*-[(1-methyl-1*H*-indol-3-yl)methyl]cyclopentane-1,3-diamine

The title compound (387 mg) was prepared from (1*S*,3*S*)-*N*-(6-fluoro-4-methylquinolin-2-yl)cyclopentane-1,3-diamine and 1-methyl-1*H*-indole-3-carbaldehyde by a method analogous to that described for Example 1 (step d).

^{1}H NMR (400 MHz, MeOH-d_4) δ 7.55-7.60 (m, 2H), 7.36 (dd, 1H), 7.27 (d, 1H), 7.23 (m, 1H), 7.13 (m, 1H), 7.07 (s, 1H), 7.01 (m, 1H), 6.58 (s, 1H), 4.46 (m, 1H), 3.88 (s, 2H), 3.70 (s, 3H), 3.35 (m, 1H), 2.42 (d, J = 0.8 Hz, 3H), 2.05-2.30 (m, 2H), 1.85-1.98 (m, 2H), 1.43-1.58 (m, 2H).

^{13}C NMR (101 MHz, MeOH-d_4) δ 159.1, 156.8, 144.8, 144.1, 137.3, 127.8, 127.2, 127.1, 123.9, 121.4, 118.8, 118.3, 117.7, 117.5, 113.5, 112.1, 109.1, 107.6, 107.4, 56.9, 51.0, 42.2, 39.5, 31.7, 31.5, 31.0, 17.5.

LC-MS $[M+H]^+$ 403.2

Example 7

N-(6-chloroquinolin-2-yl)-N'-(3-thienylmethyl)cyclohexane-1,3-diamine

a) N-(6-chloroquinolin-2-yl)cyclohexane-1,3-diamine

2,6-dichloroquinoline (198 mg, 1.0 mmol,) and cyclohexane-1,3-diamine (457 mg, 4.0 mmol) were refluxed in pyridine (10 mL) for 48 h. The solvent was evaporated and the residue was purified on a pre-packed SiO_2-column (Isolute, 10 g) eluted with DCM:MeOH (containing 1 % NH_4OH aq) 10:1 to yield 100 mg (36.3 %) of the title compound.

^{1}H NMR (500 MHz, MeOH-d_4) δ 7.72-7.67 (m, 1H), 7.55-7.50 (m, 2H), 7.41-7.38 (m, 1H), 6.80 (d, 1H, minor isomer), 6.71 (d, 1H, major isomer), 4.38 (bs, 1H, minor isomer), 3.98 (m, 1H, major isomer), 3.04 (m, 1H, minor isomer), 2.79 (m, 1H, major isomer), 2.25 -1.01 (m, 8H).

b) N-(6-chloroquinolin-2-yl)-N'-(3-thienylmethyl)cyclohexane-1,3-diamine

Pol-BH_3CN, (190 mg, 1.0 mmol) was suspended in 0.6 mL of DCM. *N*-(6-chloroquinolin-2-yl)cyclohexane-1,3-diamine (55 mg, 0.2 mmol) dissolved in 1.2 mL of MeOH:DCM 3:1, thiophene-3-carbaldehyde (22 mg, 0.2 mmol) dissolved in 0.6 mL MeOH:DCM 1:1 and 0.06 mL HOAc were added. The mixture was heated in a microwave oven at 100 °C for 10 minutes. The reaction mixture was cooled, filtered and evaporated. The residue was

purified on a pre-packed SiO_2-column (Isolute, 5 g) eluted with DCM:MeOH (containing 1 % NH_4OH aq) 10:0.5 to yield 20 mg (26 %) of the title compound as a mixture of stereoisomers.

^1H NMR (500 MHz, MeOH-d_4) δ 7.75-7.70 (m, 1H), 7.58-7.52 (m, 2H), 7.43-7.38 (m, 1H), 7.37-7.35 (m, 1H, major isomer), 7.29-7.27 (m, 1H, minor isomer), 7.27-7.25 (m, 1H, major isomer), 7.14 (m, 1H, minor isomer), 7.11 (dd, 1H, major isomer), 7.05 (dd, 1H, minor isomer), 6.8 (d, 1H, minor isomer) 6.72 (d, 1H, major isomer), 4.4 (m, 1H, minor isomer), 3.98 (m, 1H, major isomer) 3.83 (s, 2H, major isomer) 3.81 (s, 2H, minor isomer), 2.89 (m, 1H, minor isomer), 2.69 (m, 1H, major isomer), 2.41-1.06 (m, 8H).

^{13}C NMR (125.6 MHz, MeOH-d_4) δ157.1, 146.5, 140.3, 136.0, 129.4, 127.7, 126.7, 126.5, 126.2, 125.6, 124.1, 122.2, 114.4, 54.8, 44.9, 38.9, 32.6, 31.6, 22.9, 19.7

Example 8

***N*-(6-chloroquinolin-2-yl)-*N'*-[(1-methyl-1*H*-pyrrol-2-yl)methyl]cyclohexane-1,3-diamine**

Pol-BH_3CN (190 mg, 1.0 mmol) was suspended in 0.6 mL of DCM. *N*-(6-chloroquinolin-2-yl)cyclohexane-1,3-diamine (55 mg, 0.2 mmol, from Example 7 Step a) dissolved in 1.2 mL of MeOH:DCM 3:1, 1-methylpyrrole-2-carbaldehyde (22 mg, 0.2 mmol) dissolved in 0.6 mL MeOH:DCM 1:1 and 0.06 mL HOAc was added. The mixture was heated in a microwave oven at 100 °C for 10 minutes. The reaction mixture was cooled, filtered and evaporated. The residue was purified on a pre-packed SiO_2-column (Isolute, 5 g) eluted with DCM:MeOH 10:2 to yield 30 mg (36 %) of the title compound as a mixture of stereoisomers.

^1H NMR (300 MHz, MeOH-d_4) δ 7.8-7.73 (m, 1H), 7.62-7.52 (m, 2H), 7.47-7.39 (m, 1H), 6.87-6.3 (m, 2H), 6.28 (m, 1H, major isomer), 6.16 (m, 1H, minor isomer), 6.06 (t, 1H, major isomer), 5.97 (t, 1H, minor isomer), 4.48 (m, 1H, minor isomer), 4.19 (s, 2H, major isomer), 4.16 (s, 2H, minor isomer), 4.07 (m, 1H, major isomer), 3.67 (s, 3H, major isomer), 3.61 (s, 3H, minor isomer), 3.42-3.18 (m, 1H), 2.70-1.23 (m, 8H).

^{13}C NMR (75 MHz, MeOH-d_4) δ156.8, 146.3, 136.1, 129.5, 126.9, 126.6, 126.5, 126.2, 124.1, 123.5, 114.3, 111.2, 107.4, 55.4, 52.9, 39.6, 36.2, 32.9, 31.8, 29.1, 22.8.

LC-MS $[M+H]^+$ 369.0

Example 9

***N*-(6-chloroquinolin-2-yl)-*N'*-(quinolin-3-ylmethyl)cyclohexane-1,3-diamine**

Pol-BH_3CN, (1 mmol, 190 mg) was suspended in 0.6 mL of DCM. *N*-(6-chloroquinolin-2-yl)cyclohexane-1,3-diamine (0.2 mmol, 55 mg, prepared as described in Example 7 Step a) dissolved in 1.2 mL of MeOH:DCM 3:1, quinoline-3-carbaldehyde (0.2 mmol, 31 mg) dissolved in 0.6 mL MeOH:DCM 1:1 and 0.06 mL HOAc was added. The mixture was heated in a microwave oven at 100 °C for 10 minutes. The reaction mixture was cooled, filtered and evaporated. The residue was purified on a pre-packed SiO_2-column (Isolute, 5 g) eluted with DCM:MeOH 20:3 to yield 27 mg (32 %) of the title compound as a mixture of stereoisomers.

^1H NMR (300 MHz, MeOH-d_4) δ 8.9 (m, 1H, major isomer) 8.87 (m, 1H, minor isomer), 8.38 (m, 1H, major isomer), 8.26 (m, 1H, minor isomer), 8.08-7.90 (m, 2H), 7.82-7.50 (m, 5H), 7.42 (d, 1H, major isomer), 7.39 (d, 1H, minor isomer), 6.78-6.70 (m, 1H), 4.44 (m, 1H, minor isomer), 4.21 (s, 2H, major isomer), 4.19 (s, 2H, minor isomer), 4.04 (m, 1H, major isomer), 3.16 (m, 1H, minor isomer), 3.02 (m, 1H, major isomer), 2.64-1.16 (m, 8H)

^{13}C NMR (75 MHz, MeOH-d_4) δ 156.8, 151.1, 146.9, 146.3, 137.1, 136.0, 130.2, 130.0, 129.5, 128.1, 128.0, 127.8, 127.3, 126.5, 126.4, 126.2, 124.1, 114.3, 55.8, 37.8, 32.3, 30.6, 22.9, 22.4, 19.7

LC-MS $[M+H]^+$ 417.00

Example 10

N^6,N^6-dimethyl-N^2-{3-[(3-thienylmethyl)amino]cyclohexyl}quinoline-2,6-diamine

a) N^2-(3-aminocyclohexyl)-N^6,N^6-dimethylquinoline-2,6-diamine

2-chloro-*N*,*N*-dimethylquinolin-6-amine (100 mg, 0.48 mmol), cyclohexane-1.3-diamine (163 mg, 1.43 mmol), palladium(II)acetate (9 mg, 0.04 mmol), BINAP (18 mg, 0.06 mmol) and 2.5 mL toluene was sealed under nitrogen in a microwave vial. The mixture was heated in a microwave oven at 150 °C for 20 minutes. The reaction mixture was cooled, filtered and the solvent was evaporated. The residue was purified on a pre-packed SiO_2-column (Isolute, 10 g) eluted with DCM:MeOH (containing 1 % NH_4OH aq) 10:2 to yield 45 mg (33 %) of the title compound as a mixture of stereoisomers.

^{1}H NMR (500 MHz, MeOH-d_4) δ 7.69 (d, 1H), 7.52 (d, 1H), 7.22 (dd, 1H), 6.85 (d, 1H), 6.64 (d, 1H), 4.03 (m, 1H, minor isomer), 3.89 (m, 1H major isomer), 3.04 (m, 1H, minor isomer), 2.90 (s, 6H), 2.78 (m, 1H, major isomer), 2.27-0.98 (m, 8H)

b) N^6,N^6-dimethyl-N^2-{3-[(3-thienylmethyl)amino]cyclohexyl}quinoline-2,6-diamine

Pol-BH_3CN (190 mg, 1.0 mmol) was suspended in 0.6 mL of DCM. N^2-(3-aminocyclohexyl)-N^6,N^6-dimethylquinoline-2,6-diamine (40 mg, 0.14 mmol) dissolved in 1.2 mL of MeOH:DCM 3:1, thiophene-3-carbaldehyde (20 mg, 0.17 mmol) dissolved in 0.6 mL MeOH/DCM 1:1 and 0.06 mL HOAc was added. The mixture was heated in a microwave oven at 100 °C for 10 minutes. The reaction mixture was cooled, filtered and the solvent was evaporated. The residue was first purified on a pre-packed SiO_2-column (Isolute, 5 g) eluted with DCM:MeOH (containing 1 % NH_4OH aq) 10:1 yielding a crude product which was further purified by automated HPLC to give 30 g (54 %) of the title compound.

^{1}H NMR (300 MHz, MeOH-d_4) δ 7.89 (d, 1H), 7.83-7.11 (m, 5H), 6.91 (d, 1H), 6.81 (d, 1H), 4.24 (s, 2H), 3.95 (m, 1H), 3.23 (m, 1H), 2.96 (s, 6H), 2.65-1.24 (m, 8H)
LC-MS $[M+H]^+$ 381.16

Example 11

(1*S*,3*S*)-*N*-[(4-chloro-1-methyl-1*H*-pyrazol-3-yl)methyl]-*N'*-(6-methoxy-4-methylquinolin-2-yl)cyclopentane-1,3-diamine

Pol-BH_3CN (190 mg, 1 mmol) was suspended in 0.6 mL of DCM. (1*S*,3*S*)-*N*-(6-methoxy-4-methylquinolin-2-yl)cyclopentane-1,3-diamine (50 mg, 0.18 mmol) dissolved in 1.2 mL of MeOH:DCM 3:1, 4-chloro-1-methyl-1*H*-pyrazole-3-carbaldehyde (27 mg, 0.18 mmol) dissolved in 0.6 mL MeOH:DCM 1:1 and 0.06 mL HOAc was added. The mixture was heated in a microwave oven at 100 °C for 10 minutes. The reaction mixture was cooled, filtered and the solvent was evaporated. The residue was purified by automated HPLC to give 24.6 mg (33 %) of the title compound.

^{1}H NMR (400 MHz, MeOH-d_4) δ 7.71 (s, 1H), 7.60 (d, 1H), 7.22 (dd, 1H), 7.18 (d, 1H), 6.71 (s, 1H), 4.48 (m, 1H), 4.05 (s, 2H) 3.88 (s, 3H), 3.86 (s, 3H), 3.69 (m, 1H), 2.55 (s, 3H), 2.38-2.26 (m, 2H), 2.21-2.05 (m, 2H), 1.78-1.63 (m, 2H).

^{13}C NMR (101 MHz, MeOH-d_4) δ 156.9, 155,6, 148.00, 143.2, 140.3,131.1, 125,3, 124.8, 121.7, 113.6, 110.1, 105.5, 58.2, 56,1, 52.4, 41.9, 39.8, 38.3, 32.3, 30.1, 19.2.
LC-MS $[M+H]^+$ 400.4

Example 12

(1*S*,3*S*)-*N*-(6-methoxy-4-methylquinolin-2-yl)-*N*'-(1,2,3-thiadiazol-4-ylmethyl)cyclopentane-1,3-diamine

The title compound (31 mg) was prepared using the procedure described for the preparation of Example 11.
^{1}H NMR (400 MHz, MeOH-d_4) δ 8.97 (s, 1H), 7.62 (d, 1H), 7.25 (dd, 1H), 7.18 (d, 1H), 6.76 (s, 1H), 4.90 (s, 2H), 4.53 (m, 1H), 3.88 (s, 3H), 3.59 (m, 1H), 2.56 (s, 3H), 2.40-2.20 (m, 2H), 2.19-2.20 (m, 2H), 1.75-1.63 (m, 2H).
^{13}C NMR (101 MHz, MeOH-d_4) δ 160.3, 157.2, 154.8, 149.3, 138.3, 137.2, 124.5, 124.0, 122,0, 113.4, 105.8, 58.4, 56.1, 52.7, 44.7, 39.1, 32.4, 30.9, 19.3.
LC-MS $[M+H]^+$ 370.4.

Example 13

(1*S*,3*S*)-*N*-(6-methoxy-4-methylquinolin-2-yl)-*N*'-[(5-pyridin-2-yl-2-thienyl)methyl]cyclopentane-1,3-diamine

The title compound (34 mg) was prepared using the procedure described for the preparation of Example 11
^{1}H NMR (400 MHz, MeOH-d_4) δ 8.48 (d, 1H), 7.84-7.77 (m, 2H), 7.62-7.58 (m, 2H), 7.29-7.17 (m, 4H), 6.70 (s, 1H), 4.5 (m, 1H), 4.29 (s, 2H), 3.88 (s, 3H), 3.69 (m, 1H), 2.55 (s, 3H), 2.36-2.27 (m, 2H), 2.21-2.03 (m, 2H), 1.80-1.65 (m, 2H).
^{13}C NMR (101 MHz, MeOH-d_4) δ 156.9, 155.7, 150.3, 147.8, 146.7, 139.9, 138.6, 130.9, 126.3, 125.5, 124.8, 123.7, 121.6, 120.4, 113.8, 105.5, 58.0, 56.1, 52.4, 46.1, 38.5, 32.3, 30.3, 19.1, 15.4, 5.4.
LC-MS $[M+H]^+$ 445.5.

Example 14

(1*S*,3*S*)-*N*-({1-[(2-chloro-1,3-thiazol-5-yl)methyl]-1*H*-indol-3-yl}methyl)-*N'*-(6-methoxy-4-methylquinolin-2-yl)cyclopentane-1,3-diamine

The title compound (31 mg) was prepared using the procedure described for the preparation of Example 11.

^{1}H NMR (400 MHz, MeOH-d_4) δ 7.74 (d, 1H), 7.59 (d, 1H), 7.55 (d, 2H), 7.51 (d, 1H), 7.30-7.14 (m, 4H), 6.68 (s, 1H), 5.59 (s, 2H), 4.51 (m, 1H), 4.39 (s, 2H), 3.88 (s, 3H), 3.81 (m, 1H), 2.54 (s, 3H), 2.43-2.11 (m, 4H), 1.90-1.66 (m, 2H).

^{13}C NMR (101 MHz, MeOH-d_4) δ 156.8, 155.8, 153.0, 147.6, 140.9, 140.8, 139.4, 137.5, 130.5, 128.8, 125.8, 124.9, 124.0, 121.8, 121.6, 119.7, 113.7, 111.0, 107.6, 105.3, 57.9, 56.0, 52.2, 43.1, 41.9, 37.5, 32.1, 29.4, 19.1.

LC-MS $[M+H]^+$ 532.5.

Example 15

(1*S*,3S)-*N*-(6-methoxy-4-methylquinolin-2-yl)-*N'*-({5-[1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]-2-thienyl}methyl)cyclopentane-1,3-diamine

The title compound (33 mg) was prepared using the procedure described for the preparation of Example 11.

^{1}H NMR (400 MHz, MeOH-d_4) δ7.56 (d, 1H), 7.23 (d, 1H), 7.17 (dd, 1H), 7.15-7.10 (m, 2H), 6.70 (s, 1H), 6.64 (s, 1H), 4.45 (m, 1H), 4.08 (s, 2H), 3.97 (s, 3H), 3.86 (s, 3H), 3.46 (m, 1H), 2.50 (s, 3H), 2.34-2.13 (m, 2H), 2.05-1.91 (m, 2H), 1.65-1.52 (m, 2H).

LC-MS $[M+H]^+$ 516.5.

Example 16

(1*S*,3*S*)-*N*-(2,2'-bithien-5-ylmethyl)-*N'*-(6-methoxy-4-methylquinolin-2-yl)cyclopentane-1,3-diamine

Pol-BH_3CN (190 mg, 1.0 mmol) was suspended in 0.6 mL of DCM. (1*S*,3*S*)-*N*-(6-methoxy-4-methylquinolin-2-yl)cyclopentane-1,3-diamine (50 mg, 0.18 mmol) dissolved in 1.2 mL of MeOH:DCM 3:1, 2,2'-bithiophene-5-carbaldehyde (36 mg, 0.18 mmol) dissolved in 0.6 mL MeOH:DCM 1:1 and 0.06 mL HOAc was added. The mixture was heated in a microwave oven at 100 °C for 10 minutes. The reaction mixture was cooled,

filtered and the solvent was evaporated. The residue was purified on a pre-packed SiO_2-column (Isolute, 5 g) eluted with DCM:MeOH 10:1 to yield 39 mg (44 %) of the title compound.

^{1}H NMR (400 MHz, MeOH-d_4) δ 7.60 (d, 1H), 7.33 (dd, 1H), 7.22 (dd, 1H), 7.18 (dd, 1H), 7.16 (d, 1H), 7.11-7.07 (m, 2H), 7.02 (dd, 1H), 6.70 (s, 1H), 4.47 (m, 1H), 4.22 (s, 2H), 3.87 (s, 3H), 3.66 (m, 1H), 2.53 (s, 3H), 2.34-2.24 (m, 2H), 2.20-2.04 (m, 2H), 1.76-1.66 (m, 2H);

LC-MS $[M+H]^+$ 450.14

Example 17

N^4,N^4-dimethyl-N^2-{3-[(3-thienylmethyl)amino]cyclohexyl}quinoline-2,4-diamine

a) N^2-(3-aminocyclohexyl)-N^4,N^4-dimethylquinoline-2,4-diamine

A mixture of 2-chloro-*N*,*N*-dimethylquinolin-4-amine (0.102 g 0.494 mmol), cyclohexane-1,3-diamine (0.141 g, 1.23 mmol), NaO^{t}Bu (0.017 g, 0.73 mmol), $Pd(OAc)_2$ (0.008 g, 0.034 mmol), and 2-(di-^{t}butylphosphino)biphenyl (0.017 g, 0.057 mmol) in toluene (1 mL) under an N_2-atmosphere was subjected to microwave heating single node 140 °C, 10 min. The reaction mixture was cooled to room temperature, diluted with EtOAc:MeOH 5:1 containing 1% Et_3N and loaded on a short (~2 cm) SiO_2 column. Elution with EtOAc:MeOH 5:1 containing 1% Et_3N gave 92 mg (65%) of the title compound as a mixture of diastereomers (~5:1).

^{1}H NMR (400 MHz, MeOH-d_4) δ 7.81 (dd, 1H), 7.55 (bd, 1H), 7.40 (ddd, 1H), 7.11 (ddd, 1H), 6.26 (s, 1H, minor isomer), 6.15 (s, 1H, major isomer), 4.33 (m, 1H, minor isomer), 3.94 (tt, 1H, major isomer), 3.06 (m, 1H, minor isomer), 2.90 (s, 6H, minor isomer), 2.88 (s, 6H, major isomer), 2.81 (tt, 1H, major isomer), 2.26 (m, 1H, major isomer), 2.08-1.00 (m, 7H).

LC-MS $[M+H]^+$ 285.3.

b) N^4,N^4-dimethyl-N^2-{3-[(3-thienylmethyl)amino]cyclohexyl}quinoline-2,4-diamine

N^2-(3-aminocyclohexyl)-N^4,N^4-dimethylquinoline-2,4-diamine (0.036 g, 0.13 mmol) in DCM:MeOH 1:1 (1.2 mL), thiophene-3-carbaldehyde (0.11 mmol, 0.012 g) in DCM (0.6 mL) and HOAc (0.060 mL) was added to Pol-BH_3CN (0.15 g, 0.6 mmol, pre-swollen in DCM, 0.6 mL). The resultant mixture was subjected to microwave heating single node 100 °C, 10 min. The resin was filtered off and washed with portions (1-2 mL) of DCM and

MeOH, and the filtrate was concentrated. The residue was dissolved in DCM (1 mL), Pol-CHO (0.1g, 0.3 mmol) added, and the slurry was stirred at room temperature for 16 h. The resin was filtered off and washed with portions (1-2 mL each) of DCM and MeOH. The filtrate was loaded on a 1 g Isolute SCX-2 ion exchange column, washed with MeOH (10 mL), and the product eluted with MeOH containing 10% Et3N to give 0.034 g (93%) of the title compound as a mixture of diastereomers (~5:1).

^{1}H NMR (400 MHz, MeOH-d_4) δ 7.84-7.80 (m, 1H), 7.55 (bd, 1H), 7.43-7.38 (m, 1H), 7.34 (dd, 1H, major isomer), 7.26-7.02 (m, 3H), 6.24 (s, 1H, minor isomer), 6.15 (s, 1H, major isomer), 4.33 (m, 1H, minor isomer), 3.94 (tt, major isomer), 3.80 (s, 2H, major isomer), 3.78 (s, 2H, minor isomer), 2.90 (s, 6H, minor isomer), 2.88 (s, 6H, major isomer), 2.86 (m, 1H, minor isomer), 2.68 (tt, 1H, major isomer), 2.36 (m, 1H, major isomer), 2.08-1.04 (m, 7H).

^{13}C NMR (101 MHz, MeOH-d_4, major isomer) δ 159.8, 159.0, 150.4, 141.6, 130.0, 128.9, 126.7, 126.2, 125.3, 123.3, 121.6, 120.5, 99.5, 55.9, 49.5, 46.1 44.2, 40.4, 34.1, 32.8, 24.1.

LC-MS $[M+H]^+$ 381.3.

Example 18

N^4,N^4-dimethyl-N^2-[3-({[2-(phenylsulfonyl)-1,3-thiazol-5-yl]methyl}amino)cyclohexyl]quinoline-2,4-diamine

N^2-(3-aminocyclohexyl)-N^4,N^4-dimethylquinoline-2,4-diamine (0.013 g, 0.046 mmol, see earlier) in DCM:MeOH 1:1 (0.6 mL), 2-(phenylsulfonyl)-1,3-thiazole-5-carbaldehyde (0.008 g, 0.03 mmol) in DCM (0.3 mL) and HOAc (0.030 mL) was added to Pol-BH_3CN (0.15 g, 0.6 mmol, pre-swollen in DCM, 0.3 mL). The resultant mixture was subjected to microwave heating single node 100 °C for 10 minutes. The resin was filtered off and washed with portions (1-2 mL) of DCM and MeOH, and the filtrate was concentrated. The residue was dissolved in DCM (1 mL), Pol-CHO (100 mg) added, and the slurry was stirred at room temperature for 16 h. The resin was filtered off and washed with portions (1-2 mL each) of DCM and MeOH. The filtrate was loaded on a 1 g Isolute SCX-2 ion exchange column, washed with MeOH (10 mL), and the product eluted with MeOH containing 10% Et_3N to give 0.010 g (61%) of the title compound as a mixture of diastereomers (~5:1).

^{1}H NMR (400 MHz, MeOH-d_4) δ 8.06-7.08 (m, 10H), 6.21 (s, 1H, minor isomer), 6.14 (s, 1H, major isomer), 4.31 (m, 1H, minor isomer), 4.07 (s, 2H, major isomer), 4.05 (s, 2H,

minor isomer), 3.91 (tt, 1H, major isomer),2.90 (s, 6H), 2.87 (m, 1H, minor isomer), 2.66 (tt, 1H, major isomer), 2.33 (m, 1H), 2.04-1.01 (m, 7H).

LC-MS $[M+H]^+$ 522.2.

Example 19

N^2-(3-{[(2,4-dimethoxypyrimidin-5-yl)methyl]amino}cyclohexyl)-N^4,N^4-dimethylquinoline-2,4-diamine

N^2-(3-aminocyclohexyl)-N^4,N^4-dimethylquinoline-2,4-diamine (0.038 g, 0.13 mmol, see earlier) in DCM:MeOH 1:1 (1.2 mL), 2,4-dimethoxypyrimidine-5-carbaldehyde (0.019 g, 0.11 mmol) in DCM (0.6 mL) and HOAc (0.060 mL) was added to Pol-BH_3CN (0.15 g, 0.6 mmol, pre-swollen in DCM, 0.6 mL). The resultant mixture was subjected to microwave heating single node 100 °C, 10 min. The resin was filtered off and washed with portions (1-2 mL) of DCM and MeOH, and the filtrate was concentrated. The residue was dissolved in DCM (1 mL), Pol-CHO (0.1 g, 0.3 mmol) added, and the slurry was stirred at room temperature for 16 h. The resin was filtered off and washed with portions (1-2 mL each) of DCM and MeOH. The filtrate was loaded on a 1 g Isolute SCX-2 ion exchange column, washed with MeOH (10 mL), and the product eluted with MeOH containing 10% Et_3N to give 0.041 g (83%) of the title compound as a mixture of diastereomers (~5:1).

^1H NMR (400 MHz, MeOH-d_4) δ 8.16 (s, 1H, major isomer), 8.11 (s, 1H, minor isomer), 7.81 (dd, 1H, minor isomer), 7.80 (dd, 1H, major isomer), 7.56-7.52 (m, 1H), 7.40 (ddd, 1H), 7.14-7.08 (m, 1H), 6.23 (s, 1H, minor isomer), 6.15 (s, 1H, major isomer), 4.33 (m, 1H, minor isomer), 4.00-3.91 (m, 7H), 3.68 (s, 2H, major isomer), 3.65 (d, 2H, minor isomer), 2.90 (s, 6H, minor isomer), 2.88 (s, 6H, major isomer), 2.85 (m, 1H, minor isomer), 2.63 (tt, 1H, major isomer, 2.35 (m, 1H, major isomer), 2.06-1.02 (m, 7H).

^{13}C NMR (101 MHz, MeOH-d_4, major isomer) δ 171.1, 166.1, 159.8, 159.0, 158.9, 150.4, 130.0, 126.3, 125.3, 121.6, 120.5, 113.9, 99.5, 56.2, 55.3, 54.7, 49.5, 44.2, 42.8, 40.6, 34.1, 32.9, 24.1.

LC-MS $[M+H]^+$ 437.3.

Example 20

3-(6-Methoxy-4-methylquinolin-2-yl)-N-methyl-N-(3-thienylmethyl)-3-azabicyclo[3.2.1]octan-8-amine

a) 3-(6-Methoxy-4-methylquinolin-2-yl)-*N*-methyl-3-azabicyclo[3.2.1]octan-8-amine

2-chloro-6-methoxy-4-methylquinoline (0.60 g, 2.89 mmol), *tert*-butyl 3-azabicyclo[3.2.1]oct-8-yl(methyl)carbamate (0.50 g, 2.07 mmol, from WO0147893), NaO^tBu (0.32 g, 3.3 mmol), palladium(II) acetate (46 mg, 0.20 mmol) and BINAP (111 mg, 0.37 mmol) in dry toluene (4.5 mL) was heated in a microwave oven 135 °C for 15 minutes. The reaction mixture was cooled to room temperature, filtered through a plug of Celite and the plug washed with EtOAc:MeOH 1:1 (500 mL). The combined filtrate was concentrated and the residue was purified by flash chromatography (SiO_2, EtOAc:n-heptane 1:2) to yield the intermediate, Boc-protected, derivative (130 mg) which was dissolved in 10 mL of EtOAc saturated with HCl(g). After stirring at room temperature for 1 h, the solvent was evaporated and the residue was dissolved in water. After washing with EtOAc, pH was adjusted to about 10 using 2 M NaOH (aq.). The aqeous phase was extracted with EtOAc. The organic phase was washed with brine, dried with Na_2SO_4, filtered and concentrated to yield the title compound (76 mg, 12%)

^{1}H NMR (400 MHz, CDCl3) δ 7.63 (d, 1H), 7.18 (dd, 1H), 7.05 (d, 1H), 6.78 (s, 1H), 3.87 (m, 2H), 3.86 (s, 3H), 3.57 (br s, ~2H), 3.33 (d, 2H), 2.85 (m, 1H), 2.52 (s, 3H), 2.48 (s, 3H), 2.31 (s br, 2H), 1.6-1.8 (m, 4H).

LC-MS $[M+H]^+$ 312.3, 313.3

b) 3-(6-Methoxy-4-methylquinolin-2-yl)-N-methyl-N-(3-thienylmethyl)-3-azabicyclo[3.2.1]octan-8-amine

Pol-BH_3CN (45 mg, ca 0.24 mmol) was suspended (swollen) in 0.3 mL of DCM. 3-(6-methoxy-4-methylquinolin-2-yl)-*N*-methyl-3-azabicyclo[3.2.1]octan-8-amine (42 mg, 0.134 mmol, from Step a) and thiophene-3-carbaldehyde (18 mg, 0.16 mmol) were dissolved in 4.5 mL of MeOH:HOAc 10:1. The solution was added to the polymer bound reducing agent and the mixture was heated in a microwave oven at 120 °C for 10 minutes. The solution was cooled, filtered, evaporated and re-dissolved in DCM:MeOH (1 mL) and loaded on a 1g Isolute SCX-2 ion exchange column which was washed with 10 mL of MeOH. Elution with 7 mL of 10% Et_3N in MeOH gave the crude title product, which was further purified by flash chromatography (SiO_2, DCM:MeOH 95:5) to yield the title compound (32 mg, 59%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, 1H), 7.20-7.26 (m, 2H), 7.08-7.10 (m, 2H), 7.02 (dd, 1H), 6.84 (s, 1H), 3.90 (s, 3H), 3.89 (m, 2H), 3.66 (s, 2H), 3.52 (dd, 2H), 2.57 (s, 3H), 2.44 (br s, ~2H), 2.36 (m, 1H), 2.20 (s, 3H), 1.74-1.83 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0, 154.7, 143.8, 143.5, 140.1, 128.67, 128.70, 125.4, 123.6, 122.4, 120.2, 110.2, 103.4, 66.7, 55.8, 54.9, 46.6, 40.7, 36.3, 26.9, 19.7.

LC-MS $[M+H]^+$ 408.3

Example 21

6-Methoxy-4-methyl-2-[5-(3-thienylmethyl)hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl]quinoline

Using a method analogous to that described in the preparation of Example 20, the title compound was prepared from 2-chloro-6-methoxy-4-methylquinoline and *tert*-butyl hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate (see WO02060902) followed by deprotection and reductive amination.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, 1H), 7.20-7.26 (m, 2H), 7.03-7.10 (m, 3H), 6.62 (s, 1H), 3.88 (s, 3H), 3.71 (m, 2H), 3.61 (s, 2H), 3.50 (dd, 2H), 2.96 (m, 2H), 2.81 (m, 2H), 2.55 (s, 3H), 2.45 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6, 154.7, 144.0, 143.7, 140.3, 128.54, 128.51, 125.6, 123.7, 122.4, 120.3, 111.5, 103.6, 60.8, 55.7, 54.6, 53.1, 41.9, 19.5.

LC-MS $[M+H]^+$ 380.3

Pharmacological Properties

MCH1 receptor radioligand binding.

Assays were performed on membranes prepared from CHO-K1 cells expressing the human Melanin concentrating hormone receptor 1 (MCH1r). Assays were performed in a 96-well plate format in a final reaction volume of 200µl per well. Each well contained 6 µg of membrane proteins diluted in binding buffer (50 mM Tris, 3 mM $MgCl_2$, 0.05 % bovine serum albumin (BSA) and the radioligand ^{125}I-MCH (IM344 Amersham) was added to give 10 000 cpm (counts per minute) per well. Each well contained 2µl of the appropriate concentration of competitive antagonist prepared in DMSO and left to stand at 30 °C for 60 minutes. Non-specific binding was determined as that remaining following incubation with 1µM MCH (Melanin concentrating hormone, H-1482 Bachem). The reaction was terminated by transfer of the reaction to GF/A filters using a Micro96 Harvester (Skatron

Instruments, Norway). Filters were washed with assay buffer. Radioligand retained on the filters was quantified using a1450 Microbeta TRILUX (Wallac , Finland).

Non-specific binding was subtracted from all values determined. Maximum binding was that determined in the absence of any competitor following subtraction of the value determined for non-specific binding. Binding of compounds at various concentrations was plotted according to the equation

$y = A+((B-A)/1+((C/x)^D)))$

and IC_{50} estimated where

A is the bottom plateau of the curve i.e. the final minimum y value

B is the top of the plateau of the curve i.e. the final maximum y value

C is the x value at the middle of the curve. This represents the log EC50 value when A + B = 100

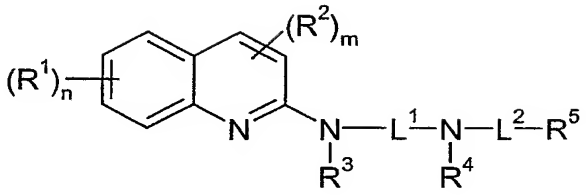
D is the slope factor. x is the original known x values. y is the original known y values.

The compounds exemplified herein had an IC_{50} of less than 2 μM in the abovementioned human MCHr binding assay. Preferred compounds had an activity of less than 1 μmolar. For example, the following IC_{50}s were obtained for the compounds of Example:Example 5, 0.026 μM, Example 16, 0.094 μM and Example 20, 0.56 μM.

Assays were also performed on membranes prepared from HEK293 cells stably expressing the rat Melanin concentrating hormone receptor 1 (MCH1r) (Lembo et al. Nature Cell Biol **1** 267-271). Assays were performed in a 96-well plate format in a final reaction volume of 200μl per well. Each well contained 5μg of membrane proteins diluted in binding buffer (50 mM Tris, 3 mM $MgCl_2$, 0.05 % bovine serum albumin (BSA) and the radioligand ^{125}I-MCH (IM344 Amersham) was added to give 10 000 cpm (counts per minute) per well. Each well contained 2μl of the appropriate concentration of competitive antagonist prepared in DMSO and left to stand at room temperature for 60 minutes. Non-specific binding was determined as that remaining following incubation with 1μM MCH (Melanin concentrating hormone, H-1482 Bachem). The reaction was terminated by transfer of the reaction to GF/A filters using a Micro96 Harvester (Skatron Instruments, Norway). Filters were washed with assay buffer. Radioligand retained on the filters was quantified using a1450 Microbeta TRILUX (Wallac , Finland).

Claims

1. A compound of formula I



I

wherein

R^1 represents a C_{1-4} alkoxy group optionally substituted by one or more fluoro, a C_{1-4} alkyl group optionally substituted by one or more fluoro, halo, cyano, a group NR^aR^b in which R^a and R^b independently represent H or a C_{1-4}alkyl group or R^a and R^b together with the nitrogen atom to which they are attached represent a saturated 3 to 7 membered heterocyclic ring optionally including an O atom (forming e.g. a morpholine ring), a group $CONR^cR^d$ in which R^c and R^d independently represent H or a C_{1-4}alkyl group or R^c and R^d together with the nitrogen atom to which they are attached represent a saturated 3 to 7 membered heterocyclic ring,

n represents 0, 1, 2 or 3 ;

R^2 represents a C_{1-4}alkyl group optionally substituted by one or more fluoro or a C_{1-4}alkoxy group optionally substituted by one or more fluoro, a group NR^aR^b in which R^a and R^b independently represent H or a C_{1-4} alkyl group or R^a and R^b together with the nitrogen atom to which they are attached represent a saturated 3 to 7 membered heterocyclic ring optionally including an O (forming e.g. a morpholine ring), a group $CONR^cR^d$ in which R^c and R^d independently represent H or a C_{1-4}alkyl group or R^c and R^d together with the nitrogen atom to which they are attached represent a saturated 3 to 7 membered heterocyclic ring;

m represents 0 or 1;

R^3 represents H or a C_{1-4} alkyl group;

L^1 represents a $(CH_2)_pC_{3-10}$ cycloalkyl group in which p is 0 or 1 and in which the cycloalkyl group may be monocyclic or bicyclic and optionally may be bridged provided that the two nitrogens bearing R^3 and R^4, respectively, are not linked to the same carbon atom, and wherein one of the carbons may be replaced by O or, alternatively, the group -$N(R^3)$ -L^1- or the group L^1-$N(R^4)$ together represent a saturated bicyclic heterocyclic ring containing from 2 to 9 carbon atoms and the nitrogen bearing R^3 or R^4 respectively or alternatively the group -$N(R^3)$ -L^1- $N(R^4)$ together represents a saturated heterocyclic ring containing from 6 to 9 carbon atoms and the nitrogens bearing R^3 and R^4 which is bicyclic;

R^4 represents H or a C_{1-4} alkyl group optionally substituted by one or more of the following: fluoro or C_{1-4} alkoxy optionally substituted by one or more fluoro;

L^2 represents an alkylene chain $(CH_2)_s$ in which s represents 1, 2 or 3 wherein the alkylene chain is optionally substituted by one or more of the following: fluoro or C_{1-4} alkyl;
or L^2 may also represent a 5-6 membered carbocyclic ring fused to R^5,

R^5 represents phenyl or naphthyl or a heterocyclic group selected from thienyl, furyl, pyridyl, pyrrolyl, quinolinyl, indolyl, benzofuranyl, benzo[*b*]thienyl, imidazolyl, benzimidazolyl, thiazolyl, thiadiazolyl, pyrimidinyl, pyrazolyl, oxazolyl, imidazo[1,2-*a*]pyridine, 5*H*-pyrrolo[2,3-*b*]pyrazine, 1*H*-pyrrolo[3,2-*c*]pyridine, 1*H*-pyrrolo[2,3-*c*]pyridine, 1*H*-pyrrolo[2,3-*b*]pyridine, *1H*-indazole wherein each R^5 is optionally substituted by one or more of the following: cyano, halo, a C_{1-4} alkyl group optionally substituted by one or more fluoro, a C_{1-4} alkoxy group optionally substituted by one or more fluoro, or by a group $S(O)_aR^y$ in which a is 0, 1 or 2 and R^y is phenyl optionally substituted by cyano, halo, a C_{1-4}alkyl group optionally substituted by one or more fluoro or a C_{1-4}alkoxy group optionally substituted by one or more fluoro, or by a group $(CH_2)_zR^z$ in which z is 0 or 1 and R^z represents phenyl or a heterocyclic group selected from thienyl, pyridyl, thiazolyl, pyrazolyl, wherein each R^z is optionally substituted by one or more of the following:cyano, halo, a C_{1-4} alkyl group optionally substituted by one or more fluoro, or a C_{1-4}alkoxy group optionally substituted by one or more fluoro;

as well as optical isomers and racemates thereof as well as pharmaceutically acceptable salts, thereof;

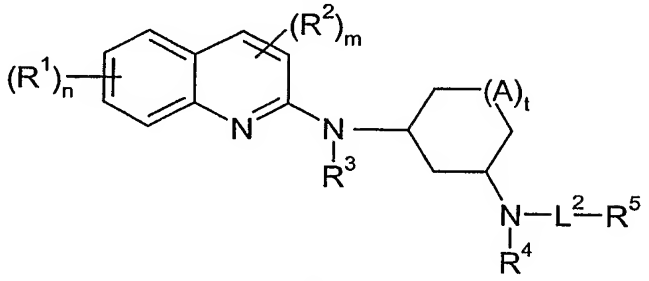
with the proviso that when

R^1 represents a C_{1-4}alkoxy group optionally substituted by one or more fluoro or a C_{1-4}alkyl group optionally substituted by one or more fluoro; and
n represents 0 or 1; and
R^2 represents a C_{1-4}alkyl group optionally substituted by one or more fluoro or a C_{1-4}alkoxy group optionally substituted by one or more fluoro ; and
m represents 0 or 1; and
R^3 represents H or a C_{1-4}alkyl group; and
L^1 represents a cyclohexyl group wherein the two nitrogens bearing R^3 and R^4, respectively, are linked to the cyclohexyl group either via the 1,3 or the 1,4 positions of the cyclohexyl group or L^1 represents a cyclopentyl group wherein the two nitrogens bearing R^3 and R^4, respectively, are linked to the cyclopentyl group via the 1,3 position of the cyclopentyl group; and
L^2 represents an alkylene chain $(CH_2)_s$ in which s represents 1, 2 or 3 wherein the alkylene chain is optionally substituted by one or more of the following: a C_{1-4}alkyl group; and
R^5 represents aryl wherein aryl means phenyl or naphthyl each of which is optionally substituted by one or more of the following: halo, a C_{1-4}alkyl group or phenyl, or
R^5 represents a heterocyclic group wherein the term heterocyclic group means thienyl, furyl, pyridyl, pyrrolyl, quinolinyl, indolyl, benzofuranyl or benzo[*b*]thienyl each of which is optionally substituted by one or more of the following: halo or a C_{1-4}alkyl group ;
or L^2 represents a C_{5-6}cycloalkyl group which is fused to an R^5 which is phenyl or a heteroaryl group selected from thienyl, furyl or pyrrolyl;
then R^4 does not represent H or a C_{1-4}alkyl group.

2. A compound as claimed in claim1 in which L^1 represents a monocyclic $(CH_2)_pC_{5-6}$ cycloalkyl group in which p is 0 or 1 wherein there are 3 carbon atoms between the two nitrogens bearing R^3 and R^4, respectively, wherein one of the carbons of the cycloalkyl group may be replaced by O or the group $-N(R^3)-L^1-$, or the group $L^1-N(R^4)$, together

represent a saturated heterocyclic ring containing from 4 to 6 carbon atoms and the nitrogen bearing R^3 or R^4 respectively.

3. A compound according to claim 1 or claim 2 of formula



IA

in which

R^1 represents chloro, fluoro, methoxy or a group NR^aR^b in which R^a and R^b independently represent H or a C_{1-4}alkyl group.

n represents 0,1 or 2 and when n=1 the substituent is attached to either position 6 or 7;

R^2 represents a C_{1-4}alkyl group or a C_{1-4}alkoxy group optionally substituted by one or more fluoro, a group NR^aR^b in which R^a and R^b independently represent H or a C_{1-4}alkyl group or R^a and R^b together with the nitrogen atom to which they are attached represent a saturated 3 to 7 membered heterocyclic ring optionally including an O (forming e.g. a morpholine ring), a group $CONR^cR^d$ in which R^c and R^d independently represent H or a C_{1-4}alkyl group or R^c and R^d together with the nitrogen atom to which they are attached represent a saturated 3 to 7 membered heterocyclic ring;

m represents 0 or 1;

R^3 represents H;

A represents CH_2 and t is 0 or 1;

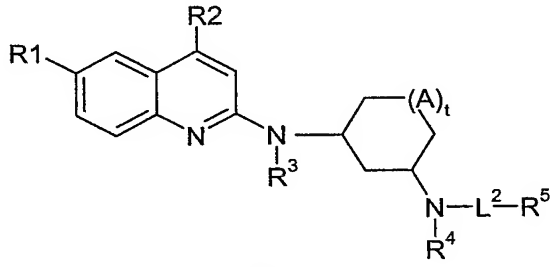
R^4 represents H;

L^2 represents CH_2, $C(CH_3)_2$ or CF_2; and

R^5 represents aryl or a heterocyclic group selected from thienyl, furyl, pyridyl, pyrrolyl, quinolinyl, indolyl, benzofuranyl, benzo[*b*]thienyl, imidazolyl, benzimidazolyl, thiazolyl, thiadiazolyl, pyrimidinyl, pyrazolyl, oxazolyl, imidazo[1,2-*a*]pyridine, 5*H*-pyrrolo[2,3-*b*]pyrazine, 1*H*-pyrrolo[3,2-*c*]pyridine, 1*H*-pyrrolo[2,3-*c*]pyridine, 1*H*-pyrrolo[2,3-*b*]pyridine, *1H*-indazole each of which is optionally substituted by one or more of the

following: cyano, halo, a C_{1-4} alkyl group optionally substituted by one or more fluoro, a C_{1-4} alkoxy group optionally substituted by one or more fluoro, or by a group $S(O)_aR^y$ in which a is 0, 1 or 2 and R^y is phenyl optionally substituted by cyano, halo, a C_{1-4}alkyl group optionally substituted by one or more fluoro or a C_{1-4}alkoxy group optionally substituted by one or more fluoro, or by a group $(CH_2)_zR^z$ in which z is 0 or 1 and R^z represents phenyl or a heterocyclic group selected from thienyl, pyridyl, thiazolyl, pyrazolyl, wherein each R^z is optionally substituted by one or more cyano, halo, a C_{1-4} alkyl group optionally substituted by one or more fluoro, a C_{1-4}alkoxy group optionally substituted by one or more fluoro as well as optical isomers and racemates thereof as well as pharmaceutically acceptable salts thereof.

4. A compound according to any previous claim of formula IB



IB

in which

R^1 represents H, methoxy, dimethylamino, chloro or fluoro;

R^2 represents H, a C_{1-4}alkyl group or a C_{1-4} alkoxy group optionally substituted by one or more fluoro, a group NR^aR^b in which R^a and R^b independently represent H or a C_{1-4}alkyl group or R^a and R^b together with the nitrogen atom to which they are attached represent a saturated 3 to 7 membered heterocyclic ring optionally including an O (forming e.g. a morpholine ring), a group $CONR^cR^d$ in which R^c and R^d independently represent H or a C_{1-4}alkyl group or R^c and R^d together with the nitrogen atom to which they are attached represent a saturated 3 to 7 membered heterocyclic ring;

R^3 represents H;

A represents CH_2 and t is 0 or 1;

R^4 represents H;

L^2 represents CH_2, $C(CH_3)_2$ or CF_2; and

R^5 represents 2-thienyl, 3-thienyl, indol-3-yl, 2-pyrrolyl, 5-pyrimidinyl, 4-thiadiazolyl, pyrazolyl, or quinolin-2-yl each of which is optionally substituted by one or more of the following: cyano, halo, a C_{1-4} alkyl group optionally substituted by one or more fluoro, a C_{1-4} alkoxy group optionally substituted by one or more fluoro and in addition when R^5 is 2-thienyl it is optionally additionally substituted by pyridyl, 2-thienyl or 3-pyrazolyl each of which is optionally substituted by halo or a C_{1-4} alkyl group optionally substituted by one or more fluoro and when R^5 is indol-3-yl it is optionally additionally substituted by 1-(thiazol-5-yl) methyl which is optionally substituted by halo.

5. A compound as claimed in any previous claim in which p is 0 and L^1 is 1,3-cyclopentyl.

6. A compound as claimed in any one of claims 1 to 4 in which p is 0 and L^1 is 1,3-cyclohexyl.

7. A compound as claimed in any either claim 5 or 6 in which the two nitrogen atoms are in a trans orientation on the cycloalkyl ring.

8. A compound as claimed in claim 7 wherein the stereochemistry of the cycloalkyl carbon atoms to which the nitrogen atoms are attached is S, S.

9. One or more of the following compounds:

N,*N*-dimethyl-2-[(3-{[(5-pyridin-2-yl-2-thienyl)methyl]amino}cyclohexyl)amino]-quinoline-4-carboxamide;

(1*S*,3*S*)-*N*-(6-chloro-4-methylquinolin-2-yl)-*N*'-[(1-methyl-1*H*-indol-3-yl)methyl]cyclohexane-1,3-diamine

(1*S*,3*S*)-*N*-(6-fluoro-4-methylquinolin-2-yl)-*N*'-(3-thienylmethyl)cyclohexane-1,3-diamine

(1*R*,3*R*)-*N*-(6-fluoro-4-methylquinolin-2-yl)-*N*'-(3-thienylmethyl)cyclohexane-1,3-diamine

(1*S*,3*S*)-*N*-(6-fluoro-4-methoxyquinolin-2-yl)-*N*'-(3-thienylmethyl)cyclohexane-1,3-diamine

(1*S*,3*S*)-*N*-(6-fluoro-4-methylquinolin-2-yl)-*N*'-[(1-methyl-1*H*-indol-3-yl)methyl]cyclopentane-1,3-diamine

N-(6-chloroquinolin-2-yl)-*N*'-(3-thienylmethyl)cyclohexane-1,3-diamine

N-(6-chloroquinolin-2-yl)-*N*'-[(1-methyl-1*H*-pyrrol-2-yl)methyl]cyclohexane-1,3-diamine

N-(6-chloroquinolin-2-yl)-*N*'-(quinolin-3-ylmethyl)cyclohexane-1,3-diamine

N^6,N^6-dimethyl-N^2-{3-[(3-thienylmethyl)amino]cyclohexyl}quinoline-2,6-diamine

(1*S*,3*S*)-*N*-[(4-chloro-1-methyl-1*H*-pyrazol-3-yl)methyl]-*N*'-(6-methoxy-4-methylquinolin-2-yl)cyclopentane-1,3-diamine

(1*S*,3*S*)-*N*-(6-methoxy-4-methylquinolin-2-yl)-*N*'-(1,2,3-thiadiazol-4-ylmethyl)cyclopentane-1,3-diamine

(1*S*,3*S*)-*N*-(6-methoxy-4-methylquinolin-2-yl)-*N*'-[(5-pyridin-2-yl-2-thienyl)methyl]cyclopentane-1,3-diamine

(1*S*,3*S*)-*N*-({1-[(2-chloro-1,3-thiazol-5-yl)methyl]-1*H*-indol-3-yl}methyl)-*N*'-(6-methoxy-4-methylquinolin-2-yl)cyclopentane-1,3-diamine

(1*S*,3S)-*N*-(6-methoxy-4-methylquinolin-2-yl)-*N*'-({5-[1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]-2-thienyl}methyl)cyclopentane-1,3-diamine

(1*S*,3*S*)-*N*-(2,2'-bithien-5-ylmethyl)-*N*'-(6-methoxy-4-methylquinolin-2-yl)cyclopentane-1,3-diamine

N^4,N^4-dimethyl-N^2-{3-[(3-thienylmethyl)amino]cyclohexyl}quinoline-2,4-diamine

N^4,N^4-dimethyl-N^2-[3-({[2-(phenylsulfonyl)-1,3-thiazol-5-yl]methyl}amino)-cyclohexyl]quinoline-2,4-diamine

N^2-(3-{[(2,4-dimethoxypyrimidin-5-yl)methyl]amino}cyclohexyl)-N^4,N^4-dimethylquinoline-2,4-diamine

3-(6-Methoxy-4-methylquinolin-2-yl)-N-methyl-N-(3-thienylmethyl)-3-azabicyclo[3.2.1]octan-8-amine

6-Methoxy-4-methyl-2-[5-(3-thienylmethyl)hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl]quinoline

and pharmaceutically acceptable salts thereof.

10. A compound of formula I as claimed in any previous claim for use as a medicament.

11. A pharmaceutical formulation comprising a compound of formula I, as defined in any one of claims 1 to 9 and a pharmaceutically acceptable adjuvant, diluent or carrier.

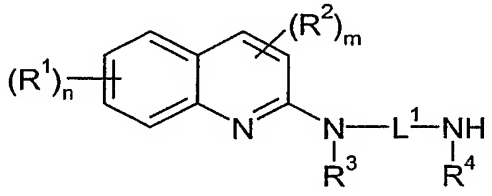
12. Use of a compound of formula I, as defined in any one of claims 1 to 9 in the preparation of a medicament for the treatment or prophylaxis of conditions associated with obesity.

13. A method of treating obesity, psychiatric disorders, anxiety, anxio-depressive disorders, depression, bipolar disorder, ADHD, cognitive disorders, memory disorders,

schizophrenia, epilepsy, and related conditions, and neurological disorders and pain related disorders , comprising administering a pharmacologically effective amount of a compound as claimed in any one of claims 1 to 9 to a patient in need thereof.

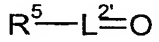
14. A compound as defined in any one of claims 1 to 9 for use in the treatment of obesity.

15. A process for the preparation of compounds of formula I comprising reacting a compound of formula II



II

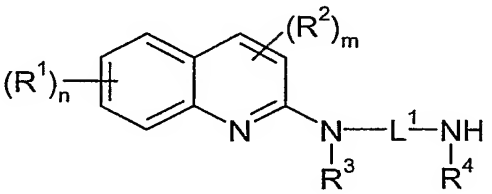
in which R^1, R^2, R^3, R^4, L^1, n and m are as previously defined with a compound of formula III



III

in which R^5 is as previously defined and $L^{2'}$ represents a group which after reaction of compounds II and III gives L^2 on reduction, under reductive alkylation conditions.

16. Intermediates of formula II



II

in which R^1, R^2, R^3, R^4, L^1, n and m are as defined in claim 1.

17. A compound of formula V selected from one or more of:

(+/-) Dibenzyl *trans*-cyclohexane-1,3-diylbiscarbamate;
(1*S*, 3*S*)-Dibenzyl-cyclohexane-1,3-diylbiscarbamate; and
(1*S*, 3*S*)-Cyclohexane-1,3-diamine dihydrochloride.

18. A method of treating obesity, type II diabetes, Metabolic syndrome and prevention of type II diabetes comprising administering a pharmacologically effective amount of a compound as claimed in any one of claims 1 to 9 to a patient in need thereof.

Abstract

Compounds of formula I, processes for preparing such compounds, their use in the treatment of obesity, psychiatric disorders, cognitive disorders, memory disorders, schizophrenia, epilepsy, and related conditions, and neurological disorders such as dementia, multiple sclerosis, Parkinson's disease, Huntington's chorea and Alzheimer's disease and pain related disorders and to pharmaceutical compositions containing them.